

FIG.

FIG. 2A

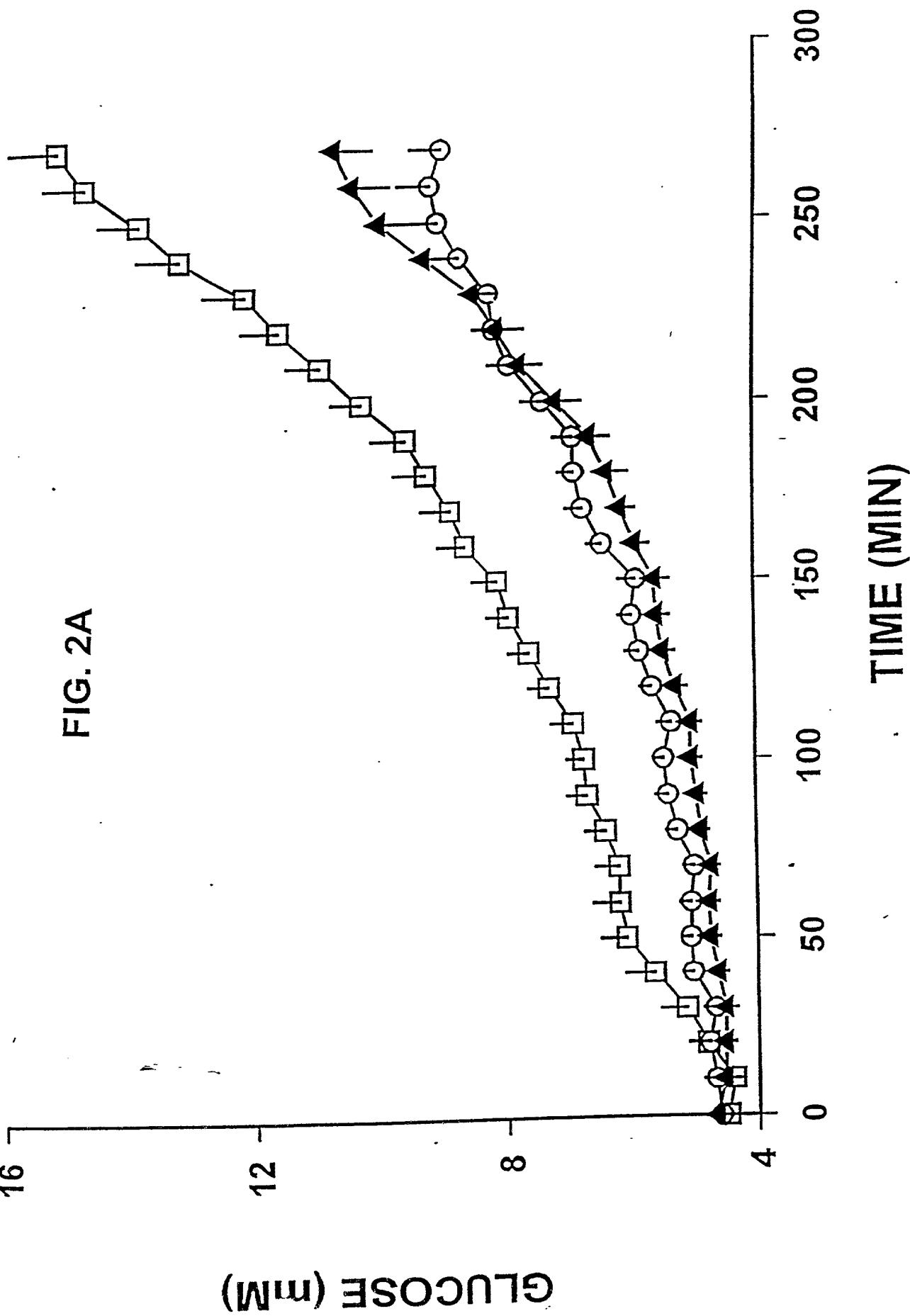


FIG. 2B

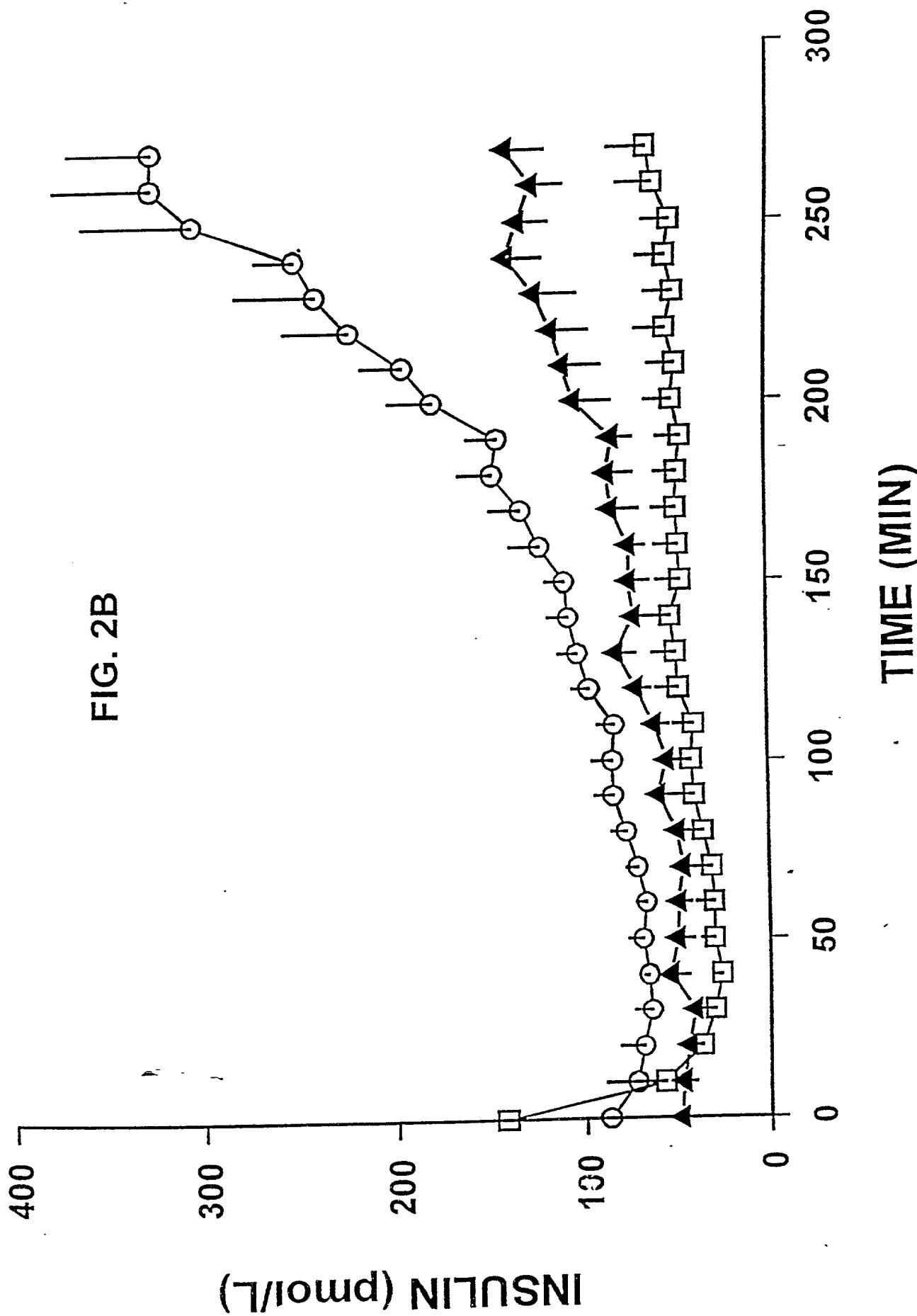


FIG. 3

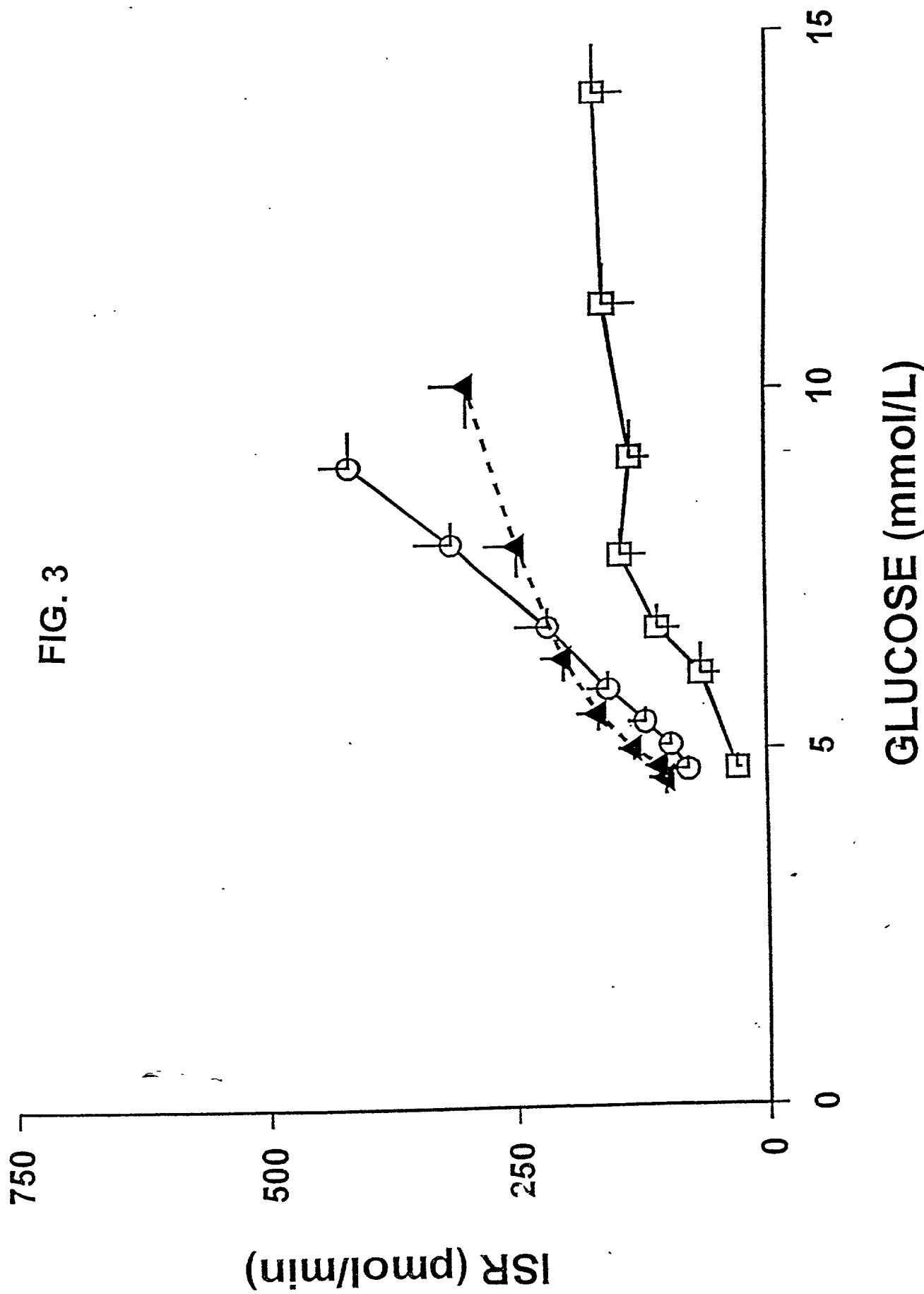


FIG. 4A

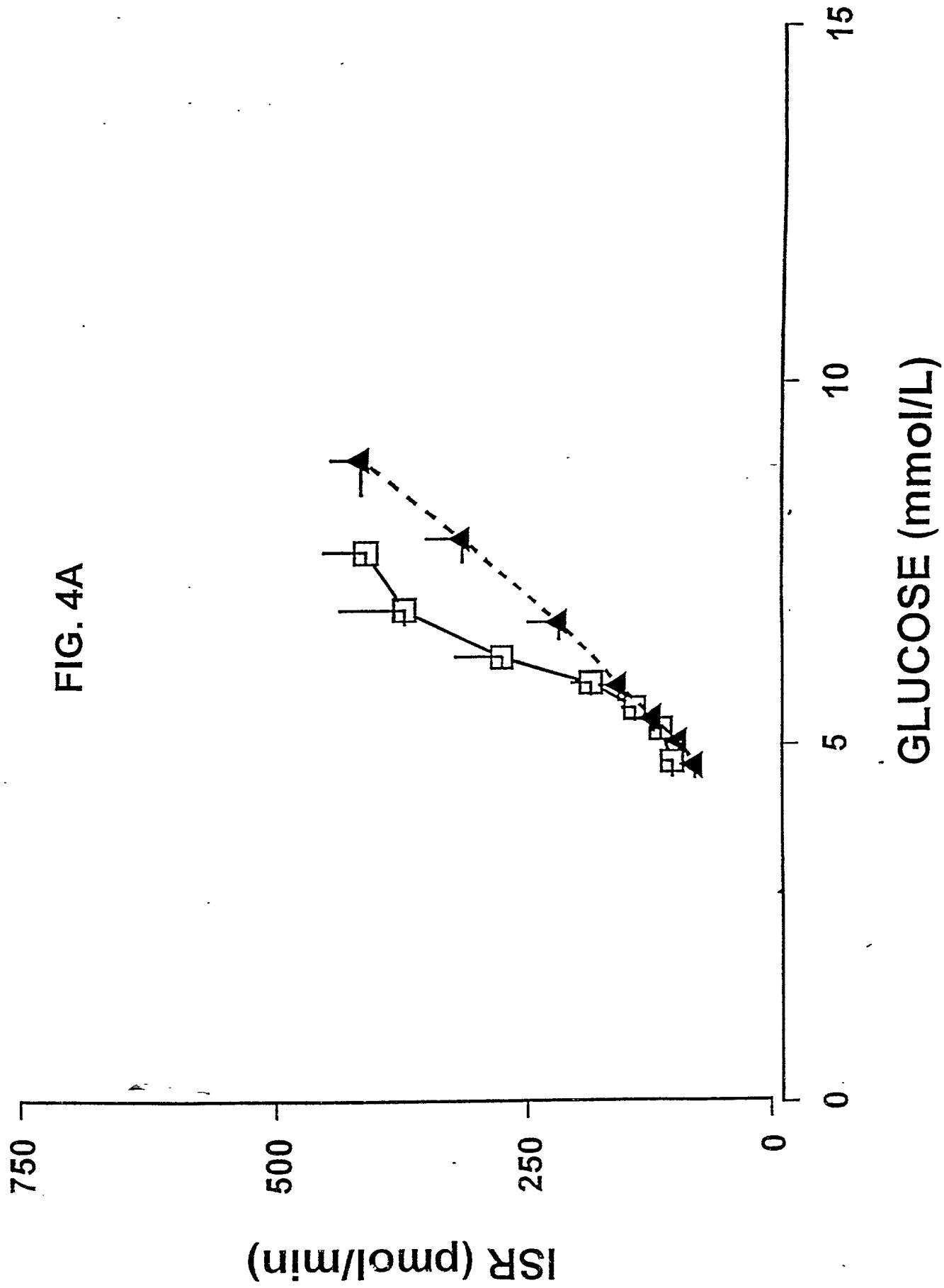


FIG. 4B

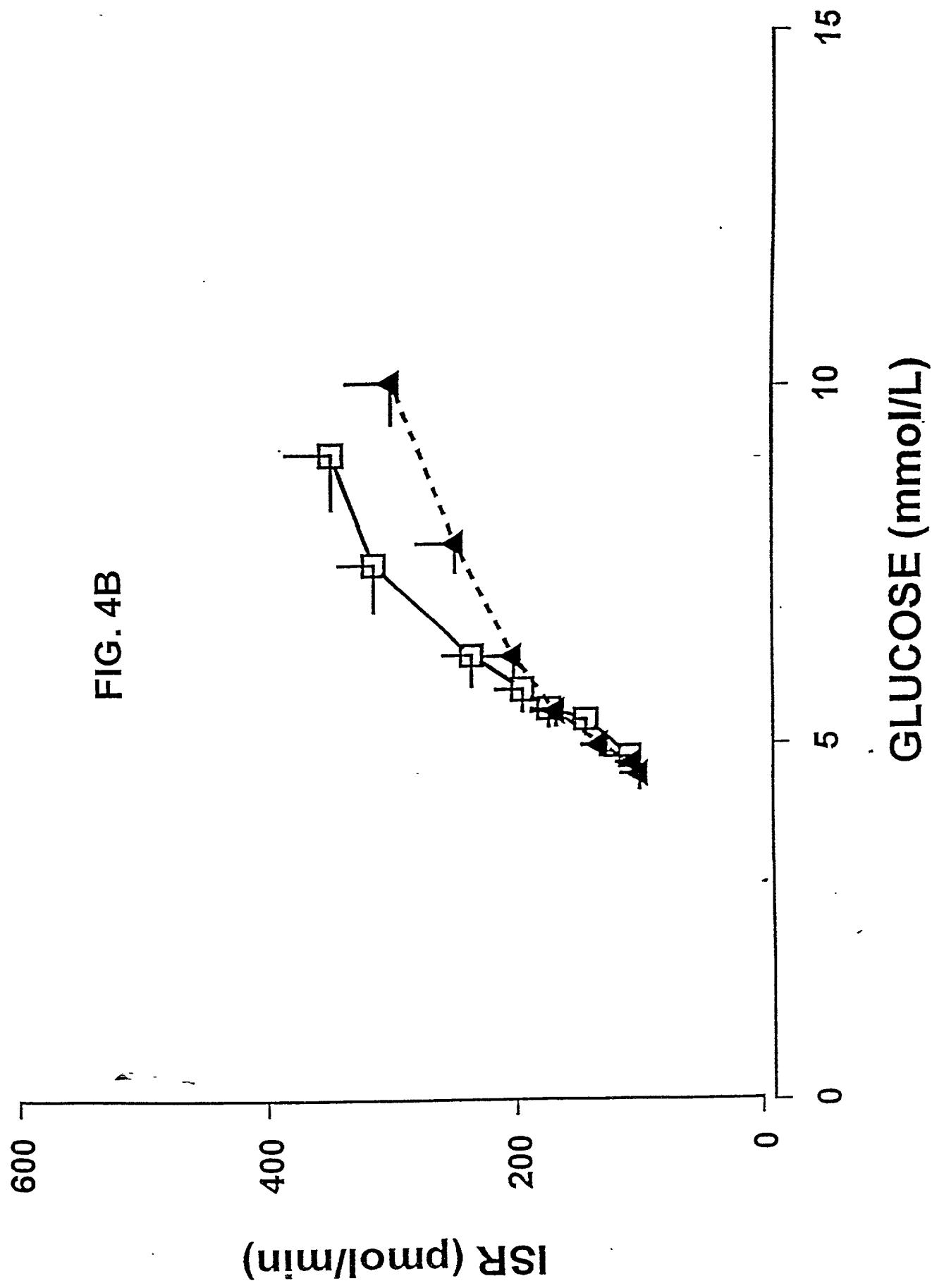
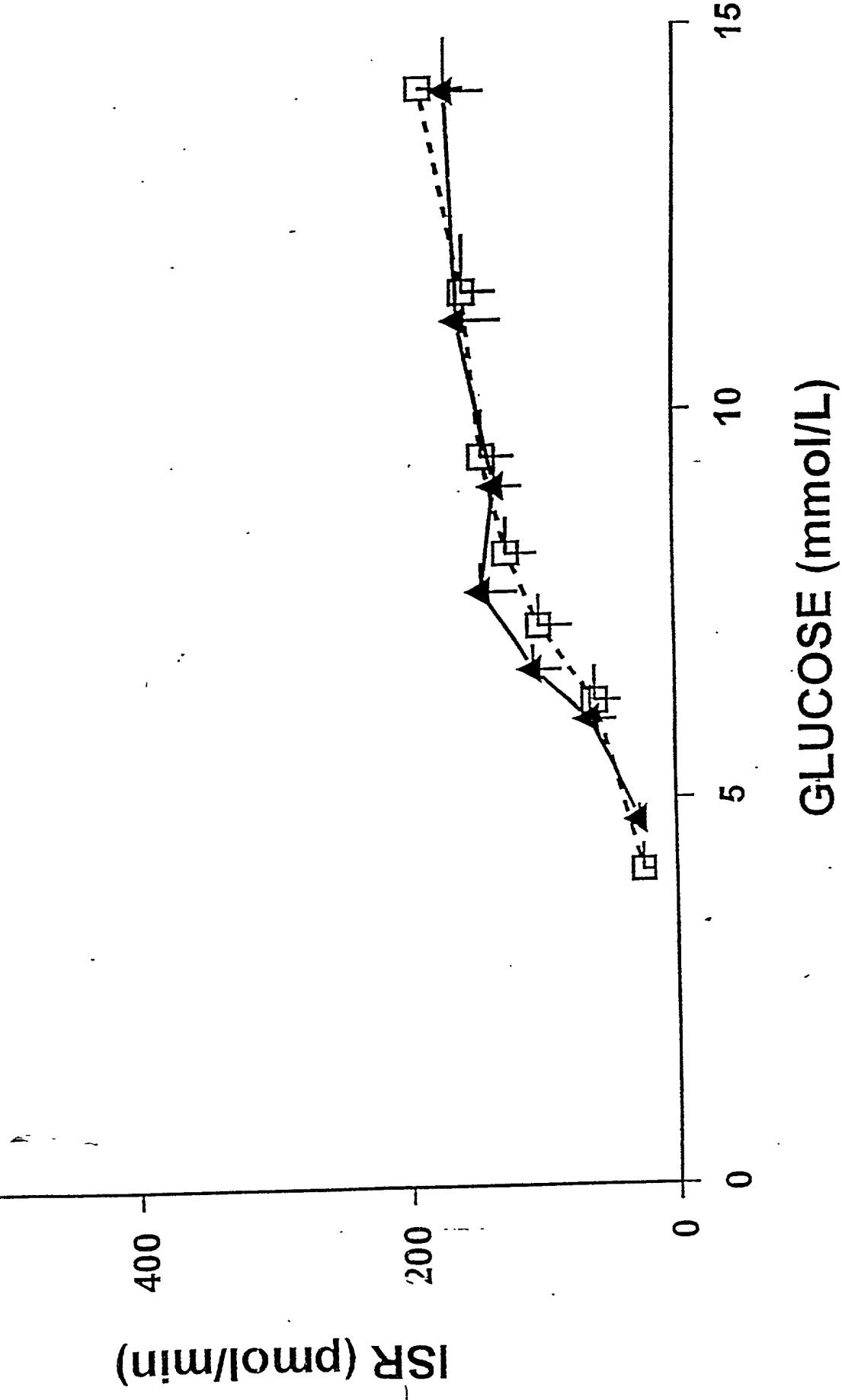
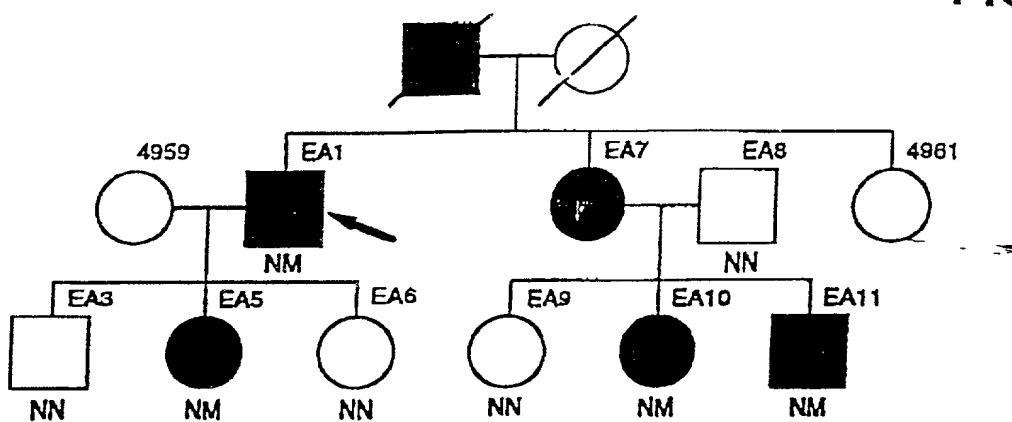


FIG. 4C



A. Edinburgh Pedigree

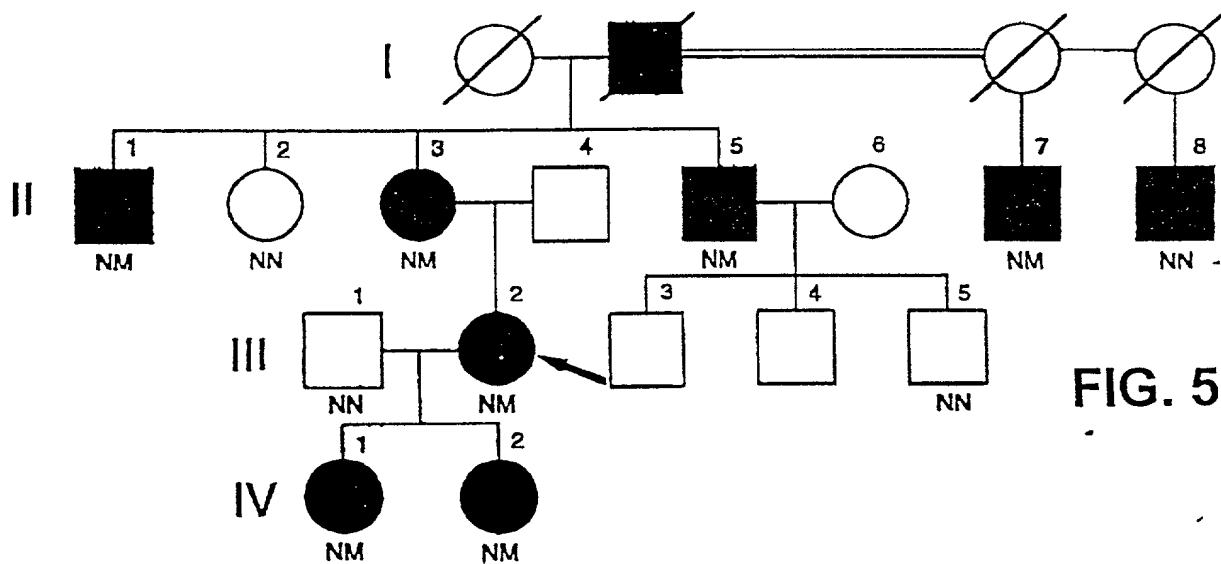
FIG. 5A



Frameshift mutation, insertion of C in codon 289, Exon 4; CCC→CCCC

B. H Pedigree

FIG. 5B



Missense mutation, codon 131, Exon 2; CGG (Arg)→CAG (Gln)

C. P Pedigree

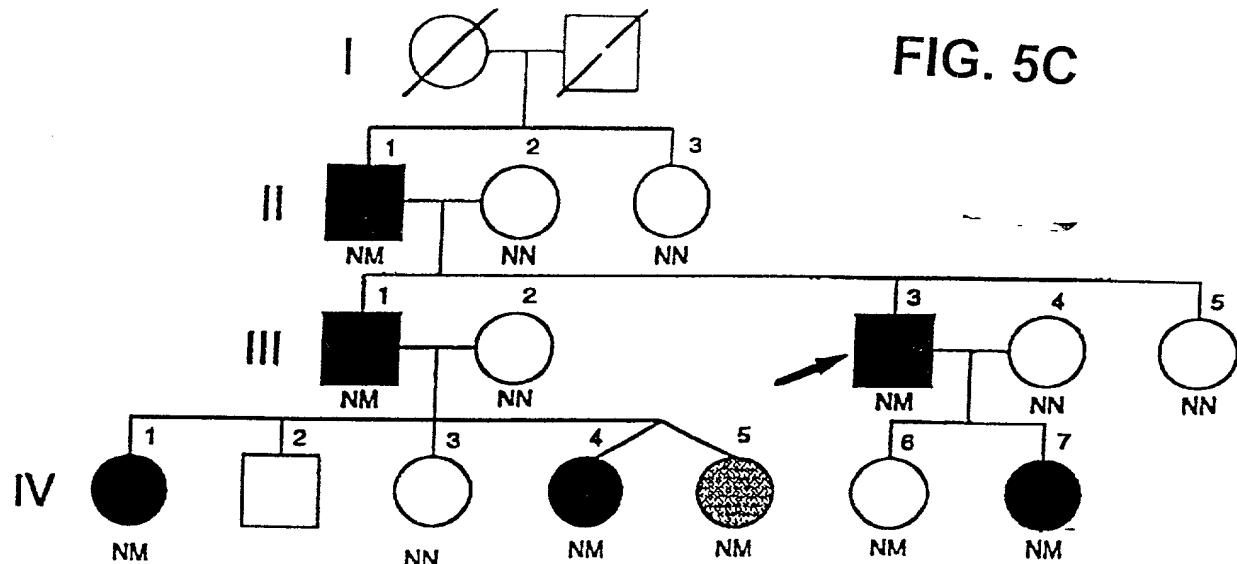


FIG. 5C

Splicing mutation - splice acceptor site of Intron 5; AG→GG

D. GK Pedigree

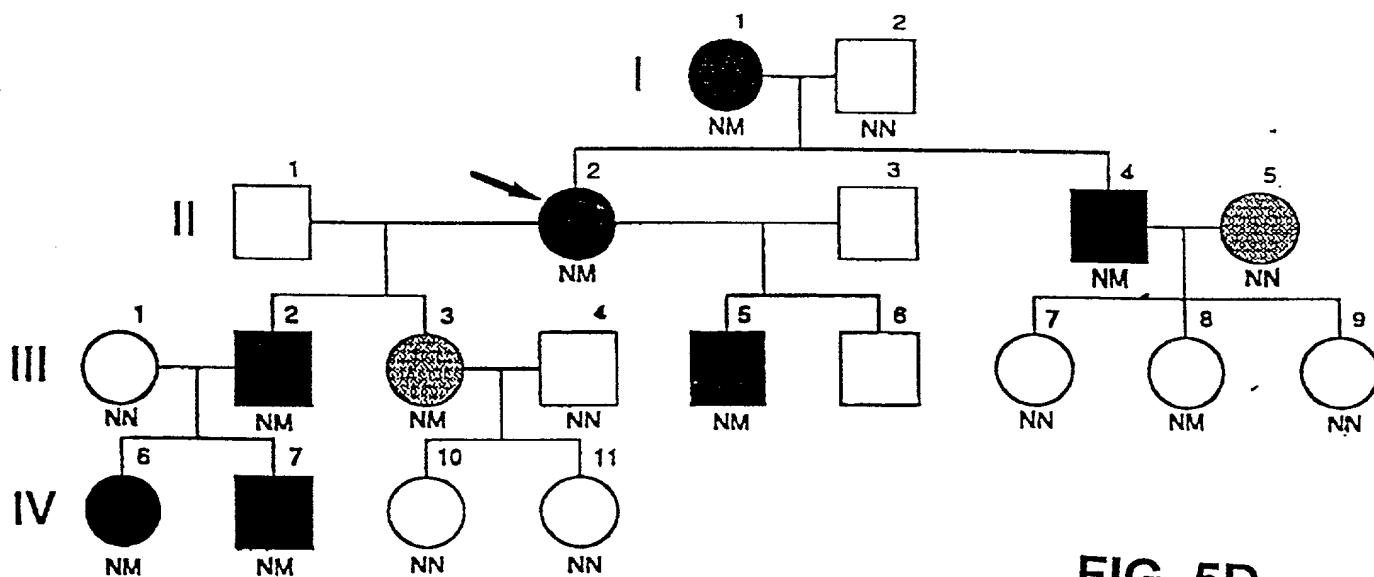


FIG. 5D

Splicing mutation - splice donor site of Intron 9; GT→AT

E. Ber Pedigree

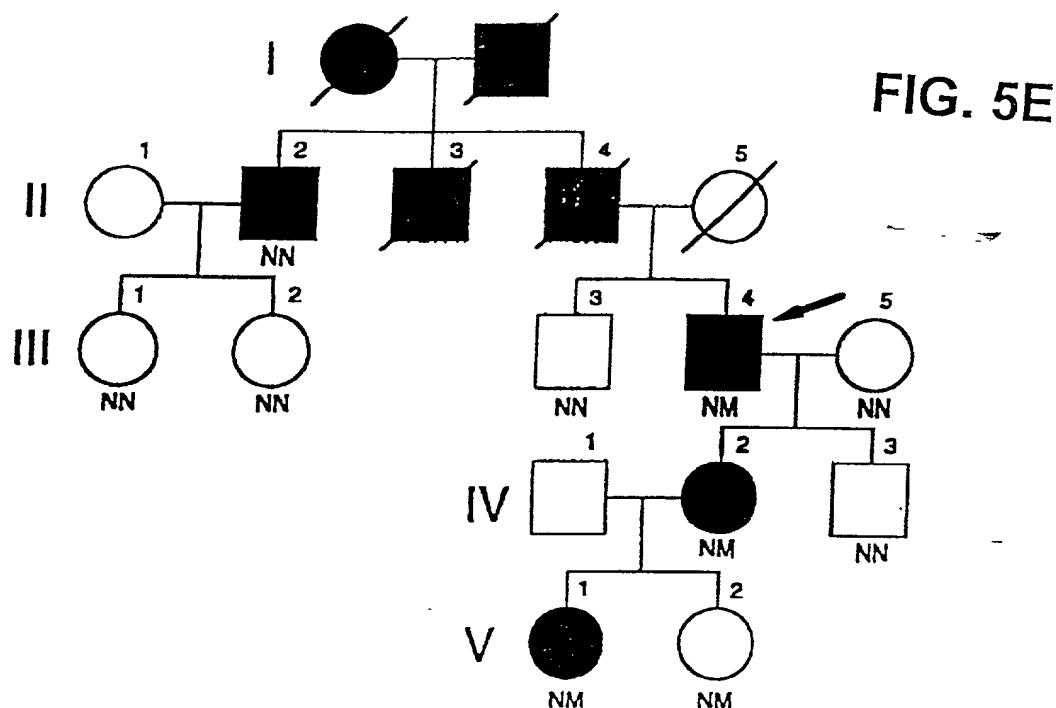


FIG. 5E

Frameshift mutation - deletion of TG in codons 547-548, Exon 9; ACT GAG→ACAG

F. A Pedigree

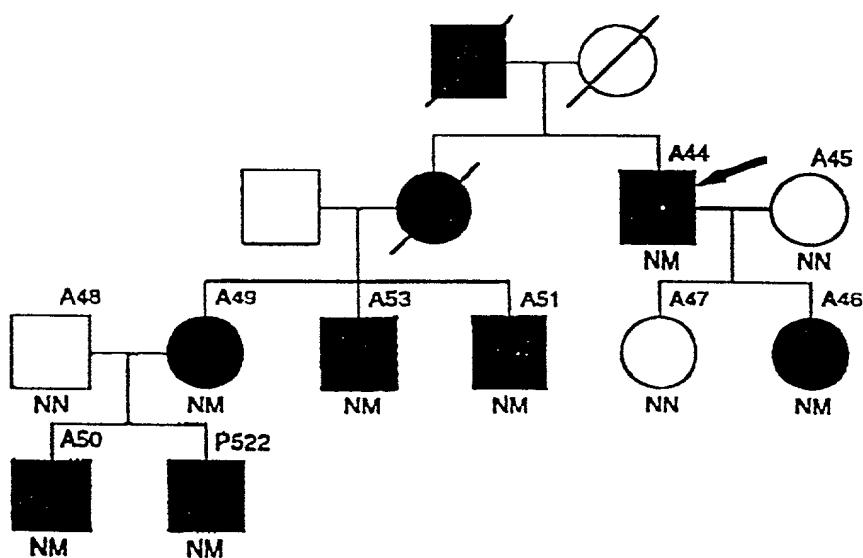
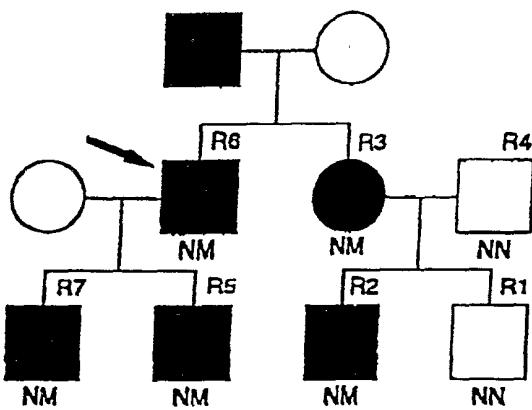


FIG. 5F

Missense mutation, codon 447, Exon 7; CCG→CTG, Pro→Leu

G. R Pedigree

FIG. 5G



Frameshift mutation - CT deletion codon 379, Exon 6; CCT \rightarrow C

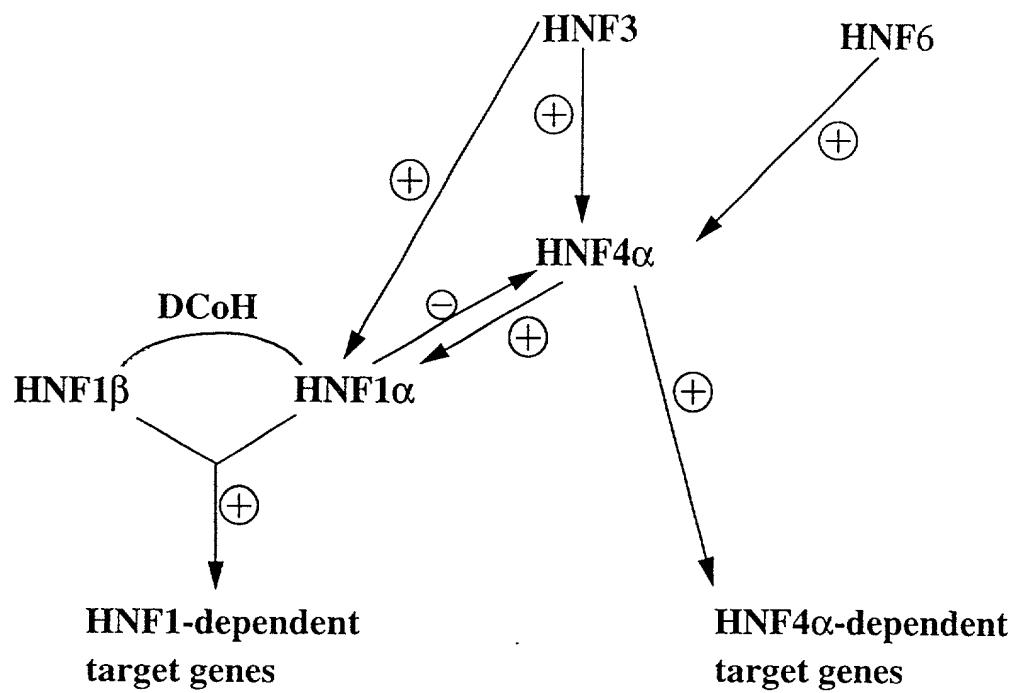


FIG. 6

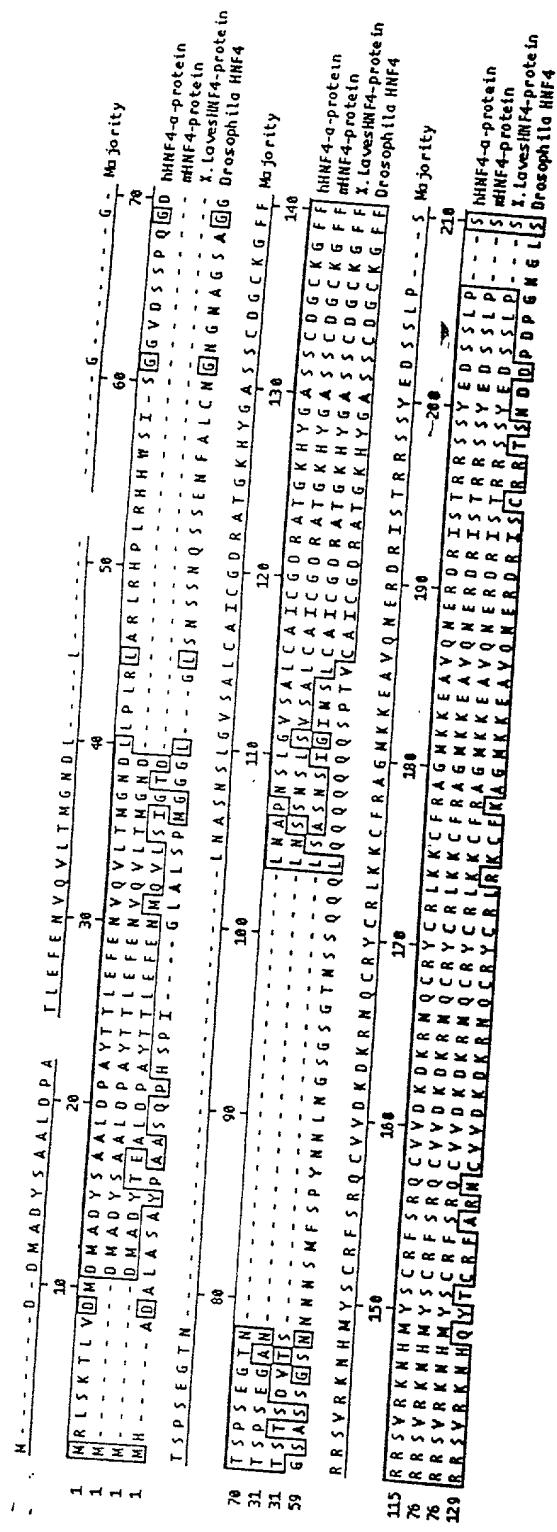


Fig. A

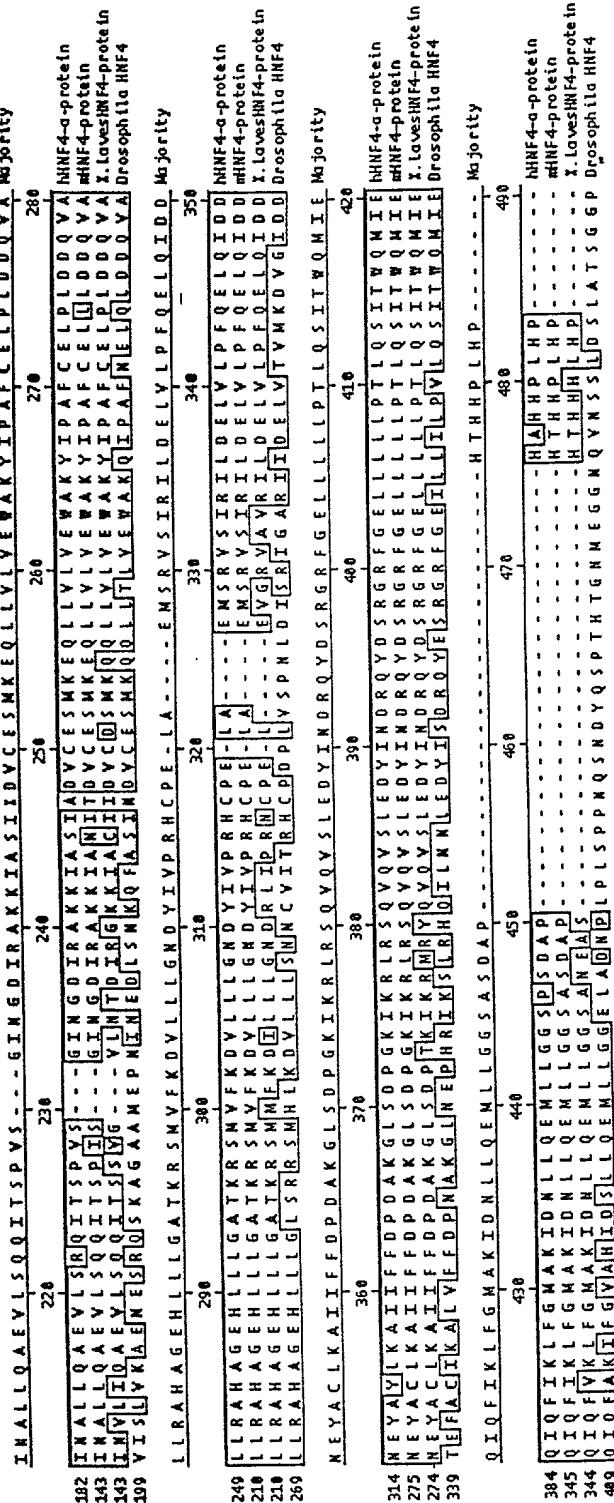


Fig. 7B

Fig. 7C

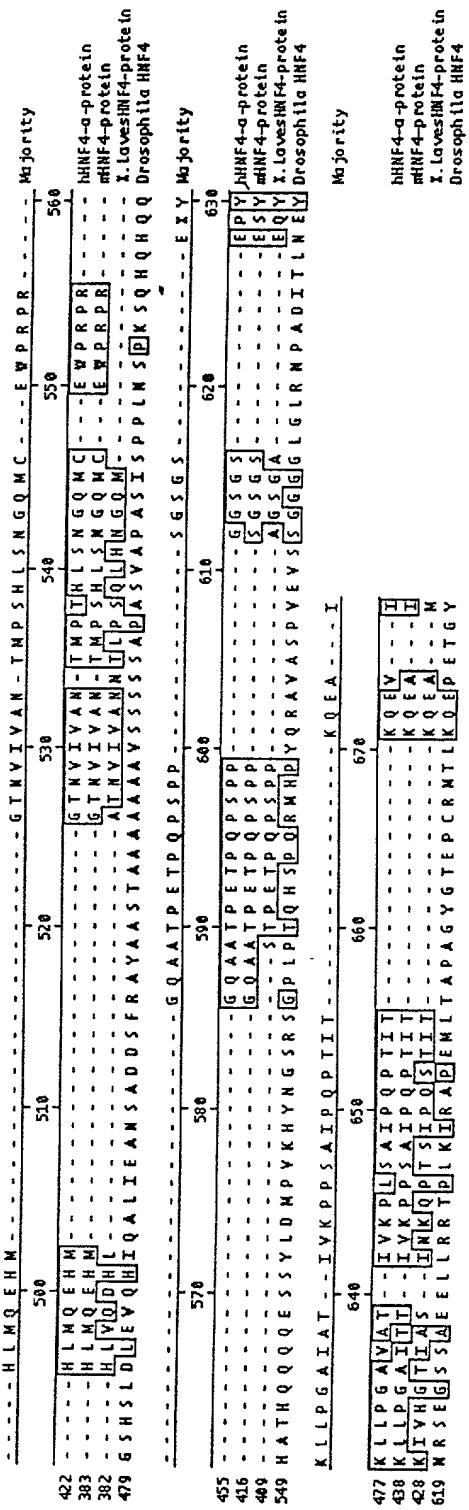


FIG. 8A. Partial Sequence of Human HNF4 Gene
(Exon 1 SEQ ID NO:34)

GCAGAGAGGG CACTGGGAGG AGGCAGTGGG AGGGCGGAGG
GCGGGGGCCT TCGGGGTGGG CGCCCAGGGT AGGGCAGGTG
GCCGCAGCGT GGAGGCAGGG AGAATGCGAC TCTCCAAAAC
CCTCGTCGAC ATGGACATGG CCGACTACAG TGCTGCAGTG
GACCCAGCCT ACACCACCCCT GGAATTGAG AATGTGCAGG

TGTTGACGAT GGGCAATGGT AGGTGGGGC AGATGTGCC
AGGTGTGCCA GTGGGGGCAG GTGTGCCTGG GTCCAGGAGC
AGATCTTGG CACTCAACTT TGGGGTGGGA GGAGAATGAT
ACAAAATGGT AGGTTGGTCC TACAGGCCAG CACAGGTGTT
GCCAAGTGAA GCCCATGTGC CCAGGCACAG TGATCACAGG

CATTCTGGT GAAGGGAGGC CTGCAAGGGC CAATTCCAG
CAAAAGTCGA TCCCGGCTAT TCCTCCCAGG CCCTTCCAGT
CCTCACTGCC TCACAGTGGC TCTGCTTGGC GCTTGGCACA
GTGACATGAT GGTGAGCTCC CCCTTGGTGC CCAGCTCCAG
CGATTCAAGCC CAGCACGGCC CCTTCGTGAA CCCCTTGGC

CTAGGTTCAAG AGAGACGGCA AGGGATGTTG TATCCCTGG
GATGGTGGTT GGAGACATAA CCGCATTCT C

FIG. 8B. Partial Sequence of Human HNF4 gene
(Exon 1b SEQ ID NO:36)

TGGATTTG TACATGTGT CTGTGTGC GGGCATAGA
GCACATGTGT TTGTGCATGC GGACCTGTTG GAGTGCCTG
TTCTCCTGC ATCTTATCC TGTATGGCG TTTGTCGTG
TGCCCATATT TGTACCTGCT GTGTATATAT GCAGTCCCT
GTGCTGCGGG CGGGGGTCAG CGGTCTCTGG TGTGCACGAC

TGCACAGACC CAAATGCAGG ACTCTGTTGT TGCCACTCAC
CAAGTGAGAT TCATATCAGC AACATGTCCG TTTGTCCTG
AGCAGATTG TTGCCGCTGC GTCTGCCAG ATTGAGGCAT
CCCCTCCGAC ATCACTGGAG CATATCTGGA GGGGTGGACA
GTTCTCCACA GGGAGGTAGG GGAAAAGAGG AGGCCCGGAA

ACCCCTCCTG GAGGGAAGAG CCCCATCGGT CCCAGGCCAG
CCTCAGAGGA GAGGGGGCAG GCAGCTGGCT GAGGTCAGCC
TYGCCACCCCTG CTTCTTCTG TGTCTGGAG CCACTCAGCC
AGTATGAGGC TGCAGCTCCA GCTGAGGTCT GGAATCTTGT
GGTCAGCTCA GCTAGGGTGA GGAGGCAGCT GCTGGGCACT

GCTTGTGTC AGCTCAGCAG GTGCTCACCT GCCCCTGCCG
TCCAGTCACG TGTGACCTTG GGCATGTCAC CTCCCCATAC
CTGGCTTCTG TATCTTCTAC AAAACAGGCT TCATTCCCCC
AGGCCTGCTG GCTGGACGGC TTTAGGCCT GTCTGAGGAC
CACGCCAGGA GCGCAAGGCA AAAACACACC AGAGAT

FIG. 8C. Partial Sequence of Human HNF4 Gene
(Exon 2 SEQ ID NO:38)

CCCCTTGCAGTTAGGAGGC CGGCTCCCAC CCCAGAAGGT
GGCCAGGTTT TCATGCCTTC CTAGAGAAAG CTGGGGCTGG
TGGCCTCCAC CACAGGGAGA CGCAGACCCCT CAGAAACAAAG
TCTGTGAAGT CACAACCAGC CCCAGTTAC AGATGTGAAA
CTGAAGCTCC AAAAAGTCAG GAGGTCACTG AGTGGGGAGG

TGATGGAGTG GAACAGCCCC CAGATCTGGC TGAGGCCGAA
GCCCTGGAGA GATCCCCGCA AGGCTCCCTT AGATGCCTGA
CATTCTGTTTC TTCCCTGAAGC CTCACTCCCT TCTCTCCTGG -
CGCAGACACG TCCCCATCAG AAGGCACCAA CCTCAACGCG
CCCAACAGCC TGGGTGTCAG CGCCCTGTGT GCCATCTGCG

GGGACCGGGC CACGGGCAAA CACTACGGTG CCTCGAGCTG
TGACGGCTGC AAGGGCTTCT TCCGGAGGAG CGTGCAGGAAG
AACCACATGT ACTCCTGCAG GTGAGGAGCC TCAATTCTT
CAGCTGGAA ATGGGCACAC TTGGGCTCAT GGCCCCAAGG
TCTGTCTTCT CCCTGAGTGG GTAGGTCCA GAGACAGCTG

CCCTTCAGGG CCTTCAAGGC TCCTTCTGGTT TTGT

FIG. 8D. Partial Sequence of Human HNF4 Gene
(Exon 3, SEQ ID NO:40)

AGAGAGTTCA TAGCACCTT CCAGCTCCTG GTGGGTTCAA
GAGAGAACTC CCGGGATGAA GAGATGAGAG CACTGAGGTT
GGGGGGTCAA CTGGATAGCC AGGGCCCTAG TTCTGTCTA
AGAGGAGGAA GTTGTGTCTT CTCCATCCAA CCATCCAAAAG
ACCTCCCCAG ATTAGCCGG CAGTGCCTGG TGGACAAAGA

CAAGAGGAAC CAGTGCCGCT ACTGCAGGCT CAAGAAATGC
TTCCGGGCTG GCATGAAGAA GGAAGGTGAG CCTCGGCCCT
CCCCGCCCA CCACCACTGC ACCACCTGCA CCCACAGCTC
CCCGACAGTC ATTTACAACGTAGCCACAC TTTATGACTC
AGTGGCAGGC CCCAGGGTGA CTGGCTAATG GCTGAGAAGA

GGGAGGGCCT GGAAATCTGA CCATAGGGAG CGGCTGGCT
TGGTCTTGAG AAAGATTG

FIG. 8E. Partial Sequence of Human HNF4 Gene
(Exon 4 SEQ ID NO:42)

tcccactcct catcagtcac agacacccccc accccctact
ccatccctgt tctccctcct caccctctg tgccctcctca
cagCCGTCCA GAATGAGCGG GACCGGATCA GCACTCGAAG
GTCAAGCTAT GAGGACAGCA GCCTGCCCTC CATCAATGCG
CTCCTGCAGG CGGAGGTCCT GTCCCGACAG GTACCAGGGT

GATCCTGCCA CCCACCCAGG GGATCCCCCA CACTACAGAG
GAGCTCACCT CCTCCACCTC CATTCTCCCC AGCCAGGCC
TGGAGCAGCT GACGGGAGGG GCCTCAGATA TTACAGAAGG
GACACTGAGT GCGGTTTCAC ATGGCCCAGT TTGCAGCAAG
GGCAGGAATC AACCTGGCG CCCTGGGGCA CTTTCTAATT

CATCCTACTG CCTGCATCCC ACAGGCCAAG CAGAGTCTTC
ACCTTCACTG AGGGCCTGCG ATCAGCTCAG CTCCGAGAGA
ACAGAGCAGT GGCTCAGTGG AGAGAGGTGG CAAAGTGGGG
CCCAGCCCTT CCCTTGCTGA GTGACCTTGG GCAAGTCACA
GCACCTCTCT GAGCCATGGT TGCCCTCATTTG TCAGAAAAGG

ATGATGATT TTTGCCTGC TTCTCCTCTA AGGCTGACAG
ACTCCTTGGG GCTCTAAAGC TG

FIG. 8F. Partial Sequence of Human HNF4 Gene
(Exon 5, SEQ ID NO:44)

TTCTCCTCA TCCCTGCCTC CTCCCTCCCT CCGTTTTAC
CCTGAGCTTC CTTCAGAGCT GGAGGGCACC CACTATCCAG
CCCCCTCCCC ACATCTGATT CCAGGGAGGG GGCTCTGTGC
AGGGGACAGA GAATGCAGGA GGGCCCGGAC ATCTCCAGCA
TTTTCTTCCC TGTATCTCTC GAAGATCACC TCCCCGTCT

CCGGGATCAA CGGCGACATT CGGGCGAAGA AGATTGCCAG
CATCGCAGAT GTGTGTGAGT CCATGAAGGA GCAGCTGCTG
GTTCTCGTTG AGTGGGCCAA GTACATCCCA GCTTTCTGCG
AGCTCCCCCT GGACGACCAG GTGAGGATGG GCGTGGATGG
TGGGCAGTAG TGGGCAGTGG GCGGGGCAGC CAGGGGGCTG

CTGGCCCACC TGGGATATAG CCGTGGACTG GCTTGATTTT
ATTTTATTAA CAAAATATG TAGTGCACAC ACGTGTCTGA
AACTTTAAAT CACCTTACAA ATATTAACCTC AGTTAGCTCC
TCCAACAACT CTATGAGGTA GGTACTAAGG TACTATTATT
ACTGCCATCT CATAGGTGAG AGATTGGGGC ACAGAGAGGT

TAAGTAACCT GCTCAAGGTC ACATAGCTAC TATCCAGCAT
AGCTGGG

FIG. 8G. Partial Sequence of Human HNF4 Gene
(Exon 6, SEQ ID NO:46)

ATTTTACAA AGCACCCCTTC ATAATTCTCC ATAGCTGGTC
CATGGGTGGG AATTGGGAC CCACAGTTT GGAACTTTT
GGGATCATAG ACCTTTTG AATCTCAAA AAAGAAAAAA
AAGCACACAG AATGTTGCTT ACAGTTCAT CAGGCACACA
GAAGAGGCC AGCACGAAGC AGTTCTTGC CCAAGGACAC

AGCAGTTCAA GGACAGAGTC AGCGCGAGGT CTCTCAGCTC
TGAGCACATG TTCTTCCCC TTCCAGGTT CTAGTTTAT
GGGTAGTAGT TTTATGATGC CCATTCACA GTTCAGGCAG
GTAGAGGCAG AGGGGAGCAT TAAGCTGACT TGCCCAGCGT
CACTGAGTTG GCTACGGCA GCCTTCCCAA GGGTACAGAT

GGCAAACACT GTTCCTTATC TCTTCAGGT GGCCCTGCTC
AGAGCCCAGT CTGGCGAGCA CCTGCTGCTC GGAGCCACCA
AGAGATCCAT GGTGTTCAAG GACGTGCTGC TCCTAGGTGA
GGCGGCTGCC TGCCCTGGCC AGGGCTCCAG GGAGGGTATG
CCTAGCATGG CACTCACCCA GGCAAGGAGA TTCACATGGT

GGCATGCAAG GGTGAGGGAG ACTAGTCAGG AGTGGCCCTG
TCCTCAGGCT TGCATTGGAG GGCTCCAGGA CTCAGTTTC
AACTGGGTAC CCCACTCAGA TGCAAGGAAA TGTGGATGCA
AGTCACCAAA TTCCCAGCAT TGAAGTCAGA GCACGATCAG
GGTTATCCCT GGAATTACCT GTGCATCCTT TTTCTTTG

ACAGAGTCTT GCTCTGTCAC TCAGGCTGGA GTGCAATGAT
GTGA

FIG. 8H. Partial Sequence of Human HNF4 Gene
(exon 7, SEQ ID NO:48)

GCAACACTAG TATTTAATA TAACAATGCT ATGAGGGAGC
TCGATTATT ATCCTCATCT TATAGATAAG AAAACTGAGG
CACAGAGAGG TTAAGTAACT TATCCAACTA TAACCAGCTA
TCAGGGGCAG AGCCATTAA GCAGGGCAGT GCAGTTCCAG
AATCTGGTCC TTTAACCTTG ATGCTTGAGT GCCTATCAGG

TGACCTTGAGT ATGTCATCGA TCTTGTGAGT CATGTTGGTA
AATGGAGCTT GGGTCATGTG AAAGAGGTCC TAGAAAGCCA
AGTTCCAAGC TCAGCCGGAT GACTCAAGGC AGCTTATCTT
CTGAATCTGG GCCTCAGCTT CCTTACCTGT GAAATGGGAG
TCACCATCCC TGCAGGTCTT CCTCCCACAG GCACCAGCTA

TCTTGCCAAC TTAAAAGCCA AAACTAGAGG AGAGGGGTCA
ACCCAAAGTG ACTTCCCATC CTCCCTCCCT CCCAACCCCTT
CCAGGCAATG ACTACATTGT CCCTCGGCAC TGCCCGGAGC
TGGCGGAGAT GAGCCGGGTG TCCATACGCA TCCTTGACGA
GCTGGTGCTG CCCTTCCAGG AGCTGCAGAT CGATGACAAT

GAGTATGCCT ACCTCAAAGC CATCATCTTC TTTGACCCAG
GTACAGTGCA CACCTCCTAA GCCATCCCTG ACTCTCTCTC
CAGAACGCTC TGCCAGACTT CTCCTATTGG GTTCTGTACA
CTGAGTTCAC AGCCTCATCT CATGTTAACG ACAGCCAGGA
GAGGCCGTTT TCATTTAACCA GATGAGGCAA GTCAAGATT

GAAGAGACAA TATGGCCGGG CGCAGTGGCT CACACCTGTA
ATCCCACATCAC TTTGGGAGGC TGAGGCAGGC GGATCACCTG
AGGTCAAGGGG TCAAGATGAG CCTGGCTAAC ATGGAGAAC
CCCATCTCTA CTTAAAA

FIG. 8I. Partial Sequence of Human HNF4 Gene (Exon 8 SEQ ID NO:50)

GTGGCTCTGC CAACAACTGG CTGTGCGACC CAGGACAAGT
CCTATCTTG CACTGTGTCT GGGTTCCCC GTGTGTAAGA
TGAGGCGGTT GCTAGGTGCT TATTGGATGC ATTCCCTCAAG
TCCC GCCCTC CATCTCCTAT TCCCCTCTCT TCTGGTTAG
TGCTTTAGGA AATGTGGCAG AAATCTTTT CTGCCTGTGT

CTAGGAAATC ATAATTCATG CTGGCGTACC CTGGTTGTTG
AGGTCCCTGA ATCCTTGTGC CCACACTGCT GAAGACTCCT
TGTGTGACAC AAGTCAGGGG ACATCTGGGT CTTGACTCCC
CAGATGCTCC AGGTGGACCC TGCTGCCCTC CCTTGCCCAC
CCTCTTCCAT TGTAGATGCC AAGGGGCTGA GCGATCCAGG

GAAGATCAAG CGGCTGCGTT CCCAGGTGCA GGTGAGCTTG
GAGGACTACA TCAACGACCG CCAGTATGAC TCGCGTGGCC
GCTTGGAGA GCTGCTGCTG CTGCTGCCCA CCTTGCAGAG
CATCACGTGG CAGATGATCG AGCAGATCCA GTTCATCAAG
CTCTCGGCA TGGCCAAGAT TGACAAACCTG TTGGAGGAGA

TGCTGCTGGG AGGTCCGTGC CAAGCCCAGG AGGGGCGGGG
TTGGATTGGG GACTCCCCAG GAGACAGGCC TCACACAGTG
AGCTCACCCC TCAGCTCCTT GGCTTCCCCA CTGTGCCGCT
TTGGGCAAGT TGCTTAACCT GTCTGTGCCT CAGTTTCCTC
ACCAGAAAAAA TGGGAACAAG GCAATGGTCT ATTTGTTCAAG

GCACCGAGAA CCTAGCACGT GCCAGTCACT GTTCTAAGTG
CTGGCAATTG AGCAAAGAAC AAGATCTTG CCCTCGGGGA
GGCTGTGTGT GTGTGATAT GTATGGATGC GTGGATATCT
GTGTATATGC CCGTATGTGC GTGCATGTGT ATATAAAGCC
TCACATTTA TGATTTGA

FIG. 8J. Partial Sequence of Human HNF4 Gene
(exon 9, SEQ ID NO:52)

GGGACACATA GATGCTATAA GTAGGTCAGT TGGCTGCAGC
AGAGATGTGG GGGATGAGGC TGAAAGGTGA GGCAGGGACCA
AATGGTTGAA GGACTTGCAC TCCAAGGAGC TTTGAGAGCC
ATTGATTACA TCCATTATGT TACTATGTGA CCAATACATT
ACTCATTAGA ACATTTACGT GATCTCAGAG CTTCCCTTATA

TGCACCTTGT TCCTTTCAAC TCACCTTGT TCTCTTGGTT
TTTGGGGTC CTCTAACAC CCTCATGAAG TCTATAGATG
GGAATGGTAC ACCCTAGTT ACTAACCCAG GAATAGGTAC
CCAACAGGCA CTGCCAATAT TGGATGGGCT GGTTGATTGG
CCACGCCCTGA GGAAGATGGC GTCCCAAGGC CTGAGGTCTG

CATCCCAGAC TCTCCATCCT GATCGACCTT CTCTACCTGC
AGGGTCCCCC AGCGATGCAC CCCATGCCA CCACCCCCCTG
CACCCCTCACC TGATGCAGGA ACATATGGGA ACCAACGTCA
TCGTTGCCAA CACAATGCC ACTCACCTCA GCAACGGACA
GATGTGTGAG TGGCCCCGAC CCAGGGGACA GGCAGGTGGG

CAAACCTCTGG GATTTACCT TGCAAAGGGT GAGGATGGGG
CTTAAGACAG GAGGCAGGAG AAAGTGGAGT CTAGAAGGTA
GAACCAGGAT GCAACAGTT TCTGGGTTCC AGGGTAGGGA
ATAAAGGGCA AGATTGTCCA TTTGTTGAGG CTGTTTATTC
AGTAAGGTGA CTGACAGCCT TTACTGAATG AAGCCATTGT

TGGGATGAGG CAATCCACTG GATGAGGTAA CCCATTGGGT
GAAGATGTCT TGGGTGAGAA TTCCATTAGT TGACATTGTC
CATTAAGTAA AAGTGGTCAT TGAAGTAAGG CTGCACAGTT
GGGTAAGGCT ATCCATTAGA CATTAGATGA GACTACCCAT
TGGGTCAGGA TGTCTGCTGG GCTA

FIG. 8K. Partial Sequence of Human HNF4 Gene
(Exon 10 SEQ ID NO:54)

TTTGGGAGAA GCAGTCCAAG TCTGCATATC AAATAAATGA
TGGAGGAGAT GGGTGGTAGG ACCTTCCAGA CCTCATAAAA
CTTAGGCTTT ATGATCTGGG ACTCACAGAA GGTTGAGCAA
TAAAAGACCT TAGGGATTAT CTGGCTTAAT TAATTCTCTC
ATTTTATAGA GGAAGAAATT AAGTCAAGGT GGGGCAGGGT

GGGAGGGGAG AACTTTCCCG GGGCTCTTCA TTTACTCCCA
CAAAGGCTGG AATTTGAGC AGCCCCTGTC TGTCTGTTG
TCCTTCCAGC CACCCCTGAG ACCCCACAGC CCTCACCGCG
AGGTGGCTCA GGGTCTGAGC CCTATAAGCT CCTGCCGGGA
GCCGTGCGCA CAATCGTCAA GCCCCTCTCT GCCATCCCCC

AGCCGACCAT CACCAAGCAG GAAGTTATCT AGCAAGCCGC
TGGGGCTTGG GGGCTCCACT GGCTCCCCCC AGCCCCCTAA
GAGAGCACCT GGTGATCACG TGGTCACGGC AAAGGAAGAC
GTGATGCCAG GACCAGTCCC AGAGCAGGAA TGGGAAGGAT
GAAGGGCCCG AGAACATGGC CTAAGGCACA TCCCACTGCA

CCCTGACGCC CTGCTCTGAT AACAAAGACTT TGACTTGGGG
AGACCCCTCA CTGCCTTGGGA CAACTTCTC ATGTTGAAGC
CACTGCCTTC ACCTTCACCT TCATCCATGT CCAACCCCCG
ACTTCATCCC AAAGGACAGC CGCCTGGAGA TGACTTGAGC
CTTACTTAAA CCCAGCTCCC TTCTCCCTA GCCTGGTGCT

TCTCCTCTCC TAGCCCCGGT CATGGTGTCC AGACAGAGCC
CTGTGAGGCT GGGTCCAATT GTGGCACTTG GGGCACCTTG
CTCCTCCTTC TGCTGCTGCC CCCACCTCTG CTGCCTCCCT
CTGCTGTCAC CTTGCTCAGC CATCCCCTCT TCTCCAACAC
CACCTCTACA GAGGCCAAGG AGGCCTTGGGA AACGATTCCC

CCAGTCATTG TGGGAACATG TTGTAAGCAC TGACTGGGAC
CAGGCACCAAG GCAGGGTCTA GAAGGCTGTG GTGAGGGAAG
ACGCCTTCT CCTCCAACCC AAC

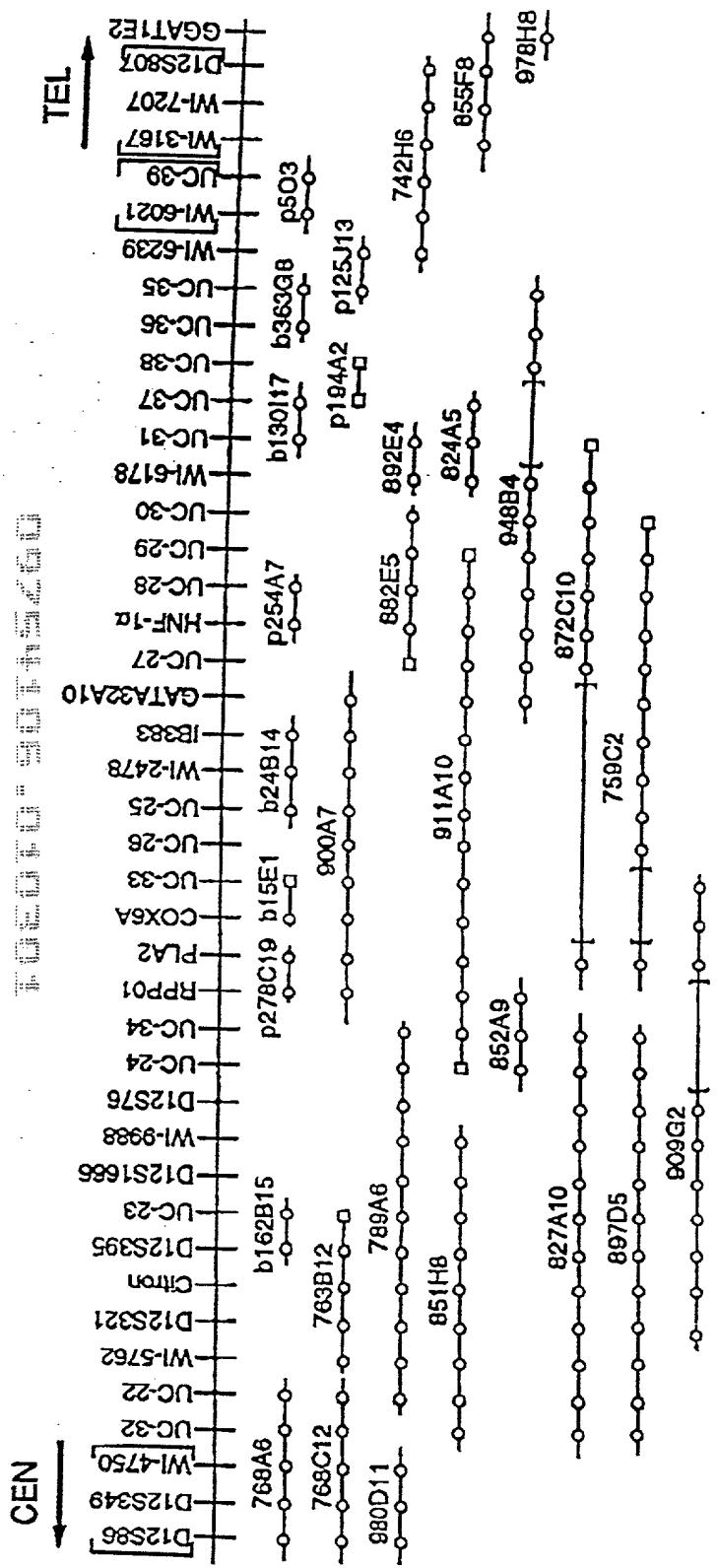


Fig. 9

Fig. 10A

Normal Allele

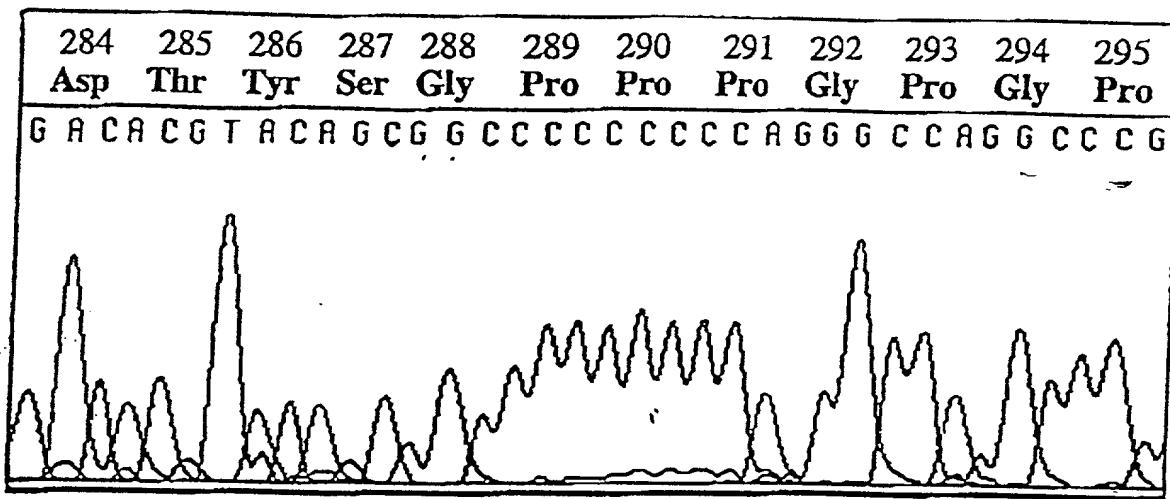


Fig. 10B

Mutant Allele

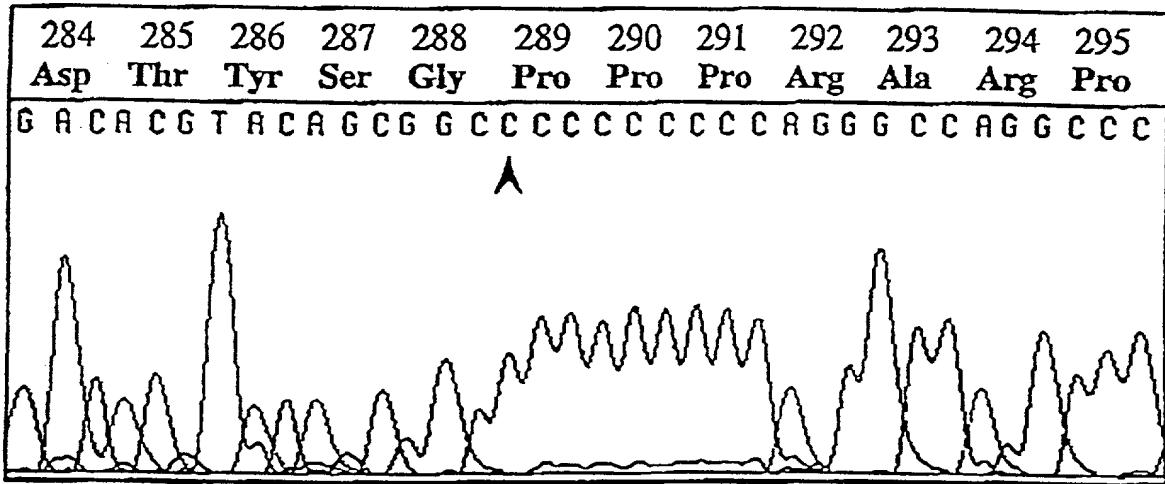


FIG. 11. Translation of human HNF1 α sequence (cDNA=SEQ ID NO:1 and protein=SEQ ID NO:2)

1 10
 20 Met Val Ser Leu Ser Gln Leu Glu Leu Leu Ala Leu Leu Ser Gly Leu Ser Lys Glu
 ...GAGCTCTGAGGAGGAGGCC ATG GTT TCT AAA CTC AGC CAG CTG CAG ACG GAG CTC CTC CTC GAG CTC GAG TCA GGG CTG AGC TCC GGT CCA
 30 40
 50 Ala Leu Ile Gln Ala Leu Gly Pro Tyr Leu Leu Ala Gly Glu Gly Pro Tyr Leu Asp Lys Gly Glu Ser Qys Gly Gly Arg
 GCA CTG ATC CAG GAA CTC GGT GAG CCG GCG CTC TAC CTC CTC GCT GAA GCA GGC CCG CTC GAC AGG GCG TCC TCC GAC GAT GGG GAA GAC TTC AGC GAC AGC GAC GAC GAT GGG GAA GAC TTC AGC GAC CCG TGG CCA CCC
 60 70
 80 Gly Glu Leu Ala Glu Leu Pro Asn Gly Leu Gly Glu Thr Arg Gly Ser Glu Asp Glu Thr Asp Asp Asp Gly Glu Asp Phe Thr Pro Pro
 'AG CTG GTT GAG CTG CCG AAT GGG CTG GGG GAG ACT CCG GGC TCC GAG GAC GAG AGC GAC GAC GAT GGG GAA GAC TTC AGC GAC CCG TGG CCA CCC
 90 100
 Exon 1 | 110 Exon 2
 Ile Leu Lys Glu Leu Glu Asn Leu Ser Pro Glu Glu Ala Ala His Gln Lys Ala Val Val Glu Thr Leu Leu Glu Asp Pro Thr Arg
 ATC CTC AAA GAG CTG GAG AAC CTC AGC CCT GAG GGG GCG CAC CAG AAA GCC GTG GTG GAG ACC CTT CTG CAG GAG GAC CCG TGG CCA CCC
 120 130 Gln (Hind- missense)

Val Ala Lys Met Val Lys Ser Tyr Leu Gln Gln His Asn Ile Pro Gln Arg Glu Val Val Val Asp Thr Thr Gly Leu Asn Gln Ser His Leu
GTC GGG AAG ATG GTC AAG TCC TAC CTG CAG CAC AAC ATC CCA CAG CCG GAG GTC GTC GAT ACC ACT GCC CTC AAC CAG TCC CAC CTG

A

150

170 Exon 2

Ser Gln His Leu Asn Lys Gly Thr Pro Met Lys Thr Gln Lys Arg Ala Ala Leu Tyr Thr Trp Tyr Val Arg Lys Gln Arg Glu Val Ala
TCC CAA CAC CTC AAC ACC AAC GGC ACT CCC ATG AAG AGC CAG AAG CAG CCG GCG GGC GGC CTC GTC ACC AGC CCT GAT GAG CTA CCA ACC AGC AAG AAC CCT GAT GAG CAG GAG CGA GAG CTA GTC GTC GCG

Exon 3

180

200

Gln Gln Pro Thr His Ala Gly Gln Gly Gln Ile Glu Glu Pro Thr Gly Asp Glu Leu Pro Thr Lys Lys Gly Arg Arg Asn Arg Pro
CAG CAG TTC ACC CAT GCA GGG CAG GCA GGG CTG ATT GAA GAG CCC ACA GGT GAT GAG CTA CCA ACC AGC CCT GAT GAG CAG GAG CGA GAG CTA GTC GTC GCG

210

220

230

Lys Trp Gly Pro Ala Ser Gln Ile Leu Phe Gln Ala Tyr Glu Arg Gln Lys Asn Pro Ser Lys Glu Glu Arg Glu Thr Leu Val Glu
AAG TGG GGC CCA GCA TCC CAG CAG ATC CTG TTC CAG CAG TAT GAG AGG CAG AAG AAG AAC CCT AGC AAG GAG GAG CGA GAG CTA GTC GTC GAG

Exon 3 | 240 Exon 4

250

260

Glu Cys Asn Arg Ala Glu Qys Ile Gln Arg Gly Val Ser Pro Ser Gln Ala Gln Gly Leu Gln Asn Leu Val Thr Glu Val Arg Val
GAG TGC ATG AGG GGG GAA TGC ATC CAG AGA GGG GTG TCC CCA TCA CAG GCA CAG GCA CAG GCA CAG GCA CAG GCA CAG GCA CTC GTC AAC GAG CTC GAG GTC GGT GTC

270

280

Tyr Asn Trp Phe Ala Asn Arg Arg Lys Glu Glu Ala Phe Arg His Lys Leu Ala Met Asp Thr Tyr Ser Gly Pro Pro Pro Gly Pro Gly

TAC AAC TCG TTT GCC AAC CCC AAA GAA GAA GGC TTC CCC CAC AAG CTC AAG TAC ATG GAC AGG

CCC (Dangue - C insertion)

CCC Pro Gly Pro Ala Leu Pro Ala His Ser Ser Pro Gly Leu Pro Pro Ala Leu Ser Pro Ser Lys Val His Glu Val Arg Gly Gin CCT GCA CCT CGG CTG CCC CCT CAC AGC TCC CCT CCA CCT GCC CTC TCC CCC AGT AGG GTC CAC G|GT GTG CCC TTT GGA CAG

330

340

Pro Ala Thr Ser Glu Thr Ala Glu Val Pro Ser Ser Gly Gly Pro Leu Val Thr Val Ser Thr Pro Leu His Glu Val Pro Thr CCT GGG ACC AGT GAG ACT GCA GAA GAA GAA GCA TCA AGC ACC GGC CCT CCC TTA GTG ACA GTG TCT ACA CCC CCT CTC CAC CAC AGC

(Pratt - mutation splice acceptor site Exon 6, AG -> GG)

360

Exon 5 | 370 Exon 6

Gly Leu Glu Pro Ser His Ser Leu Leu Ser Thr Glu Ala Lys Leu Val Ser Ala Ala Gly Pro Leu Pro Pro Val Ser Thr Leu Thr GGC CTG GAG CCC ACC CAC ACC CTG CTG AGT ACA GAA GCA AGG CTG GCT GGC TCA GCA CCT CCC CCT CTC ACC CCT GTC AGC ACC CTG ACA

C- (Newton - CT deletion)

Ala Leu His Ser Leu Glu Glu Thr Ser Pro Gly Leu Asn Glu Glu Pro Glu Asn Leu Pro Gly Val Met Thr Ile GCA CTG CAC AGC TTG GAG CGG ACA TCC CCC CCT CTC ACC CCT CTC ATC ATG GGC TCA CCT GGG GTC ATG ACC ATC

420

430

Exon 6 | Exon 7 440

Gly Pro Gly Pro Ala Ser Leu Gly Pro Thr Pro Thr Thr Asn Thr Gly Ala Ser Thr Leu Val Ile Gly Leu Ala Ser Thr Gln Ala Gln
GGG CCT CCT GGG CCT ACC TCC CTG CCT ACC TCC GGT GTC ATC GCA GGT ACA AAC ACC ACC TTC GTC ACC CTC GAG CTC TCC AGC TCC ACG CAG GCA CAG

450

470

460

Ser Val Pro Val Ile Asn Ser Met Gly Ser Ser Leu Thr Thr Leu Gln Pro Val Gln Pro Ser Gln Pro Leu His Pro Ser Tyr Gln Gln
AGT GTG CCG GTC ATC AAC ACC ATG GGC AGC CTC ACC ACC CTC GAG CAG AGC ACC CCT GTC CAG CTC TCC CAG CTC TAC CAG CAG

480

490

Exon 7 500 | Exon 8

Pro Leu Met Pro Pro Val Gln Ser Pro Pro Met Ala Thr Met Ala Gln Leu Gln Ser Pro His Ala Leu Tyr Ser
CCC CTC ATG CCA CCT GTG CAG AGC CAT GTG ACC CAG CAC CTC ACC ATG CTC ATG CCT CAG CTC AGC ACC ACC GAC ACC ATG CTC ATC ACC GAC ACC ACC GAC CTC TCC AGT GAG CAG GCA TCT CAG AGC GGC CTC GGC

510

520

530

His Lys Pro Glu Val Ala Gln Tyr Thr His Thr Gly Leu Leu Pro Gln Thr Met Leu Ile Thr Asp Thr Thr Asn Leu Ser Ala Leu Ala
CAC AAG CCC GAG GTG GTC GGC CAG TAC ACC CAC AGC CTC CCG CAG ACT ATG CTC ATC ACC GAC ACC ACC GAC ACC ATG CTC ATC ACC GAC ACC ACC GAC CTC TCC AGT GAG CAG GCA TCT CAG AGC GGC CTC GGC

Exon 8 540 | Exon 9

550

560

Ser Leu Thr Pro Thr Lys Gln Val Pro Thr Ser Asp Thr Glu Ala Ser Ser Glu Ser Gly Leu His Thr Pro Ala Ser Gln Ala Thr Thr
AGC CTC ATG CCG ACC ACC AAG CAG GTC TTC ACC TCA GAC ACT GAG GGC TCC AGT GAG CAG GCA TCT CAG AGC GGC ACC ACC

570

580

Exon 9 | 590 Exon 10

Leu His Val Pro Ser Gln Asp Pro Ala Gly Ile Gln His Leu Gln Pro Ala His Arg Leu Ser Ala Ser Pro Thr Val Ser Ser Ser Ser

CCTGGCTGGCTGGGAGTTCCAAACCCCTGGAGCTCTGAGGACTGGCAGGCTGAAACCTGTAAGGAAAGGATGTCCCCACATGCTCTGGCTGC

TCCTGAGAACCTGGCTCTAGTGACCGGCTTACCCCTGGATTCAAGGAAAGGCTGGGTAAGGAAACCCCTGAACTTGAGCCAGGGAGCTGGAGTTATTAACT

TTTAACTAACTCAAGGAGAAATGGGGTG

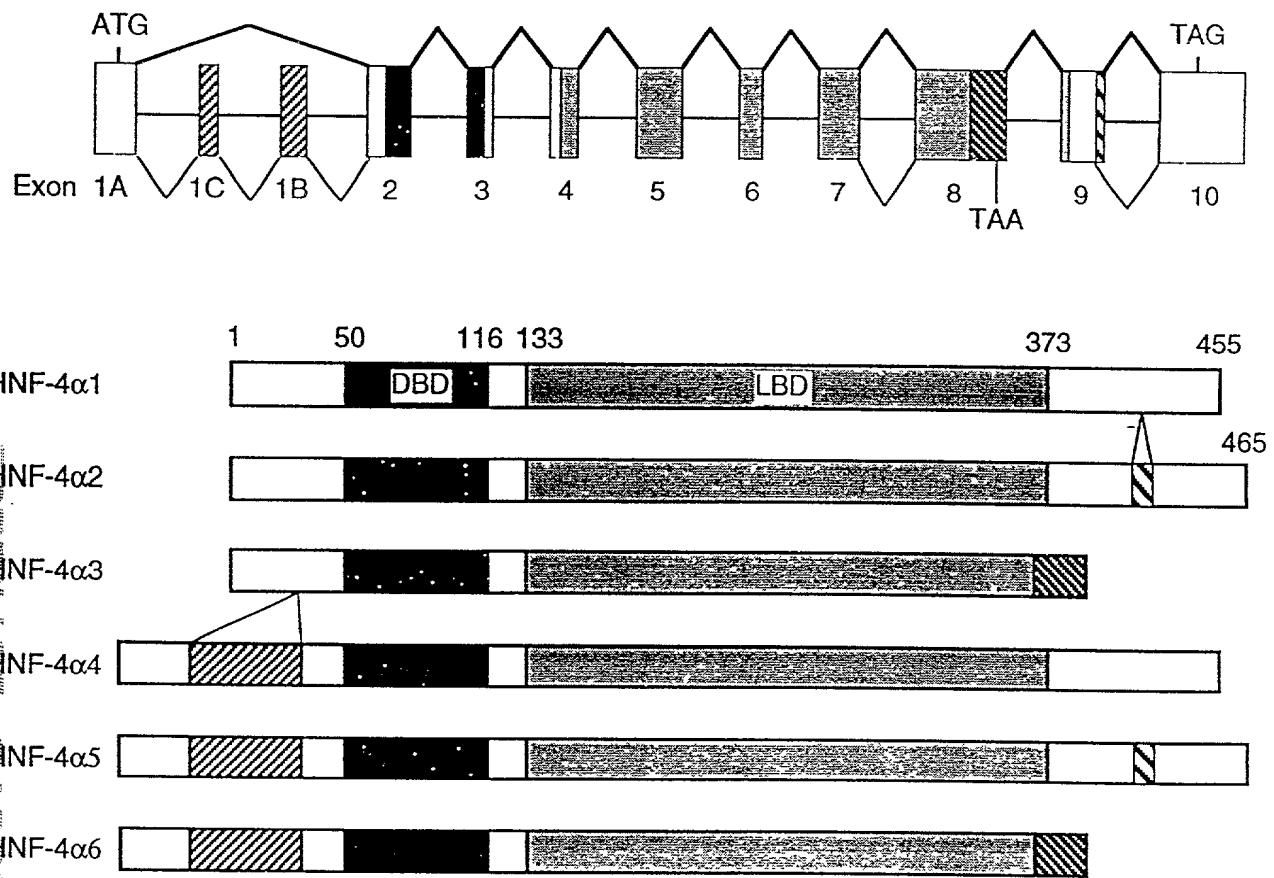


Fig. 12

human T G G G C C T G G G A T T A G G T T T C T A A A T C G T G G C C A T G G G C A G C C T T A T 618
 mouse T G G G - C T T G G G T G T T A G G T T C A G T T C A G C G A C C C A G G A C A G C T T A T

 human C T C T G C A A A A G C A I T T G A G G G T A G A A G T C A T G A T T T G G A A G T T A T G A A HNF-6 668
 mouse C T C - - - A A A - - - T G A G G A T A G G A T G A A G T C A T G A T C T G G A C C T G A T T G G C

 human T T A G G G G A T C T C G G A G G T A G G C T - G T C A G T G C C T G A T A G T A T A G A 717
 mouse T T A G G G G C T T C A T A G T G G C T T G C C A G T G T C T A A A C A T G T C A G C T G G G

 human A T G C C T G A C T T G G G G T G A C A A T G G C T T G G A G G G T G G G T C A A G G G - 766
 mouse T T G T C A C C T T G - - G T G A - - G A C T T G G - - G G G C T G C T G A G G C A A G G G

Fig. 13A

Fig. 13B

human G A T C T T C C A G A G G A C G G T T T G A A G - - - G A A G G C A G A G A G G C A C - T T G 1052
 mouse G A G T C T C C C A G A G G A C A G T T T G A A A G A G A A G G A A G G A A G G A A G G A C C T G

 human G G A G G A G G C A G T G G G A G G G C G G A G - - - G G C G G G G C C C - - - - - T T C G G 1091
 mouse G A G G G C A G G G G G A G G G G G G G G G G G G G G G G G G G G G G G G G G C T G G G G C T C A G C C C C A G

 human G G - - T G G G C G - - - C C C A G G - - - G T A G G G C A G G T G G C C G C G G G C G T G G A 1130
 mouse G G C T T G G G T G G G C A T C C T G G G C C G G G C A G A C A G G G G C T A A G G C G G G G G G G G G G G G

 human G G C A G G G A G A T G C G A C T C T C C A A A A C C C T C G T C G A C A T G G C A C A T G 1176
 mouse T A - G G G G A G A T G C G A C T C T C T A A A A C C C T T G C C G G C A T G G A T A T G G A T A T G

Fig. 13C

Normal Allele

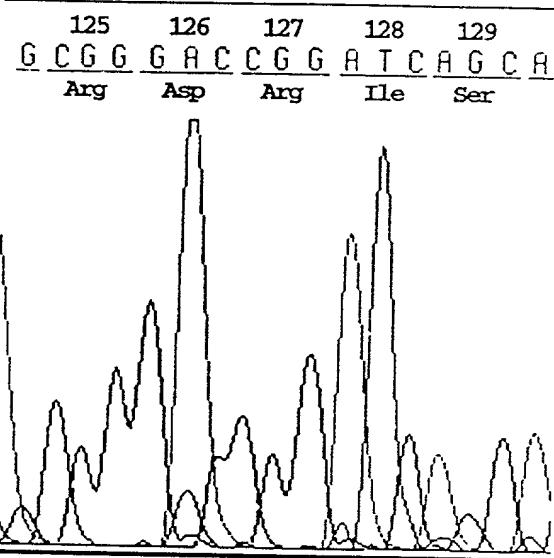


Fig. 14A

Mutant Allele

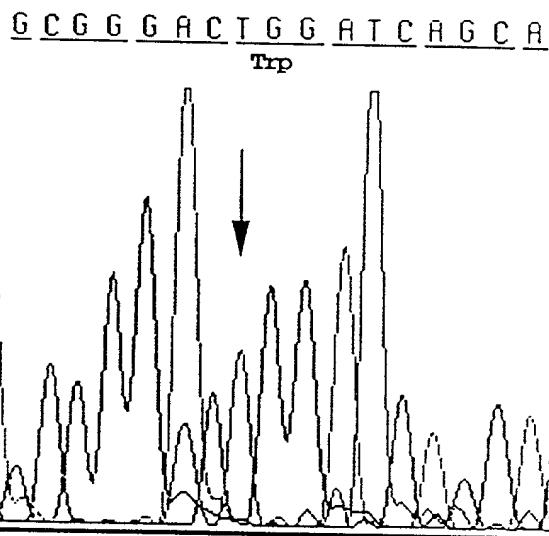
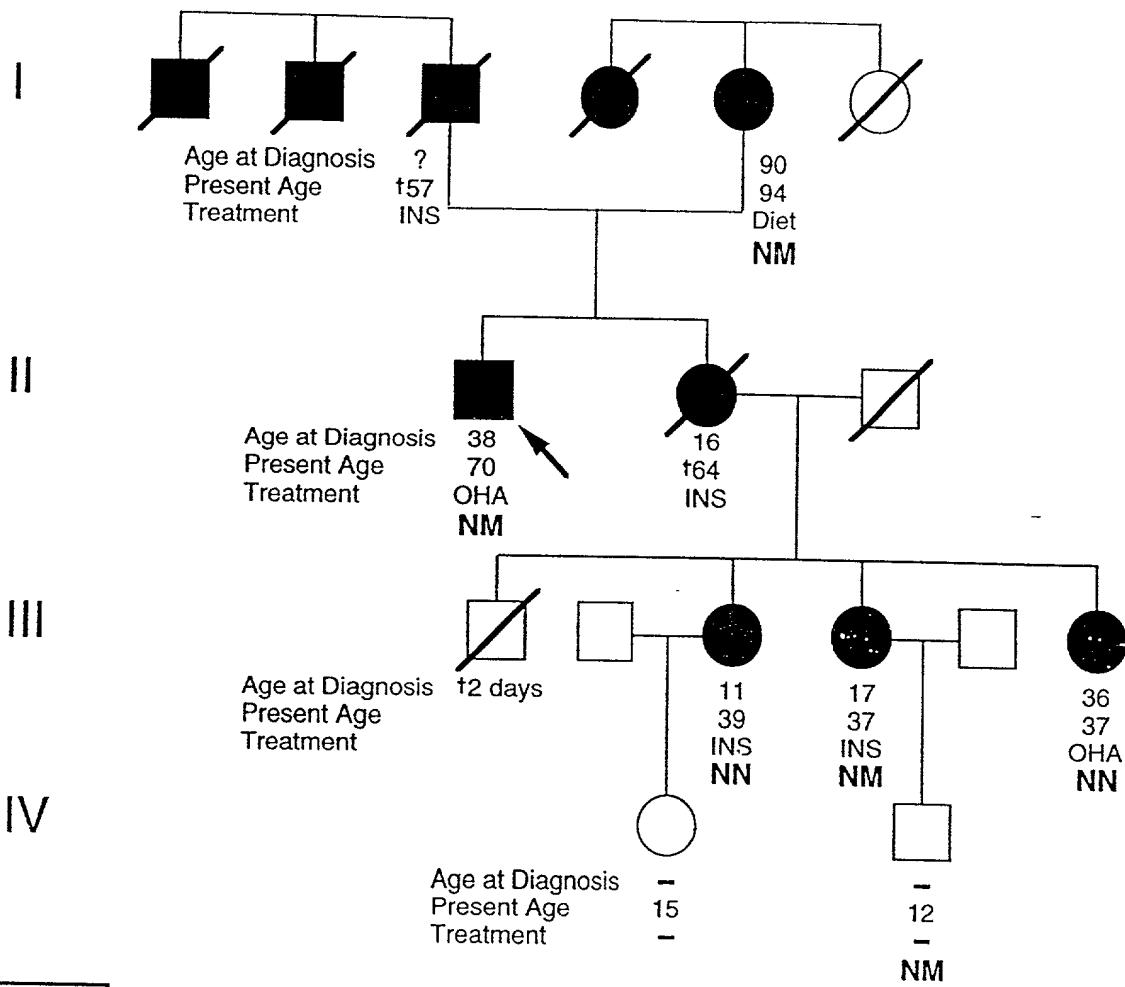


Fig. 14B

J2-21



J2-96

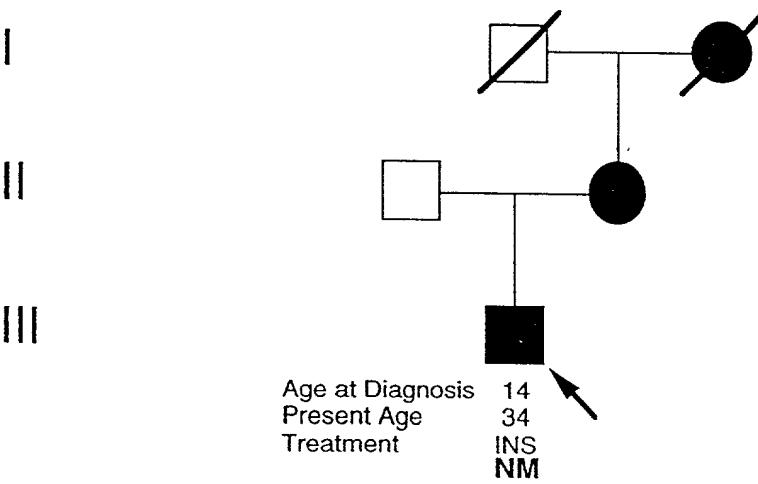


Fig. 15

Fig. 16

I

Age at Diagnosis
Present Age
Present Therapy
Complications

D20S96
D20S43
D20S169
HNF-4 α
D20S89
D20S119
D20S424

44 years	-
64 years	-
Insulin	-
R, M, N	-
8 2	8 4
6 6	1 6
3 1	3 3
M N	N N
1 6	9 10
6 1	1 8
5 15	8 10

II

Age at Diagnosis
Present Age
Present Therapy
Complications

D20S96
D20S43
D20S169
HNF-4 α
D20S89
D20S119
D20S424

28 years	18 years
47 years	37 years
OHA	Insulin
-	R
1 4	8 4
6 6	6 6
3 3	3 3
M N	M N
1 10	1 10
6 8	6 8
5 10	5 10
2 4	1 9
6 4	6 1
5 10	5 8

III

Age at Diagnosis
Present Age
Present Therapy
Complications

D20S96
D20S43
D20S169
HNF-4 α
D20S89
D20S119
D20S424

17 years 14 years
18 years 14 years
OHA -

8 1	8 8
6 6	6 6
3 3	3 3
M N	M N
1 3	1 7
6 2	6 4
5 6	5 11

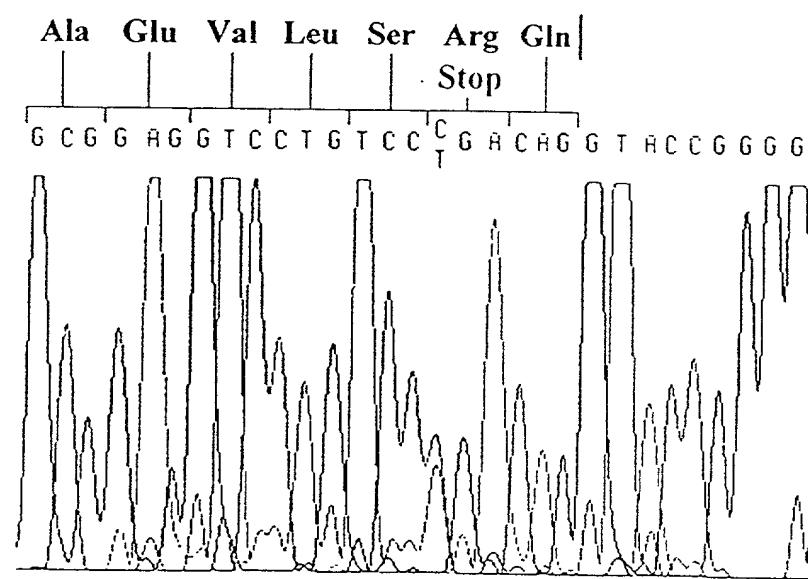


Fig. 17

Fig. 18A

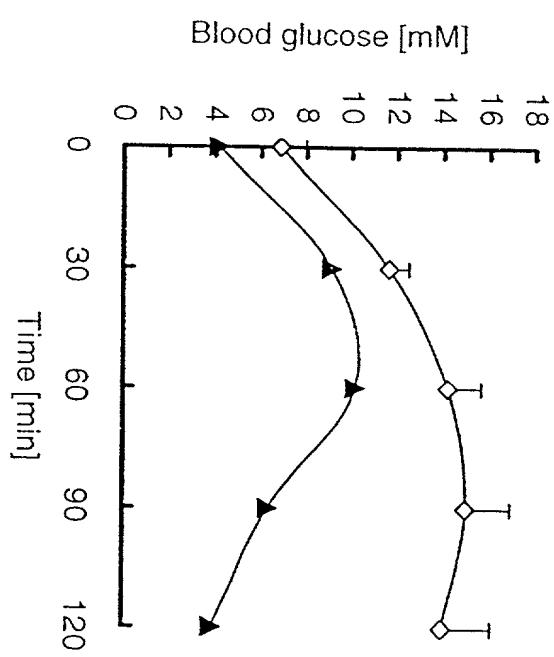


Fig. 18B

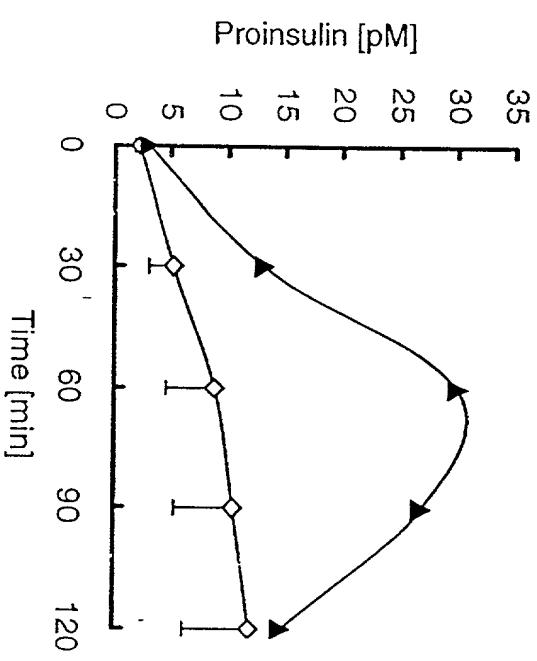
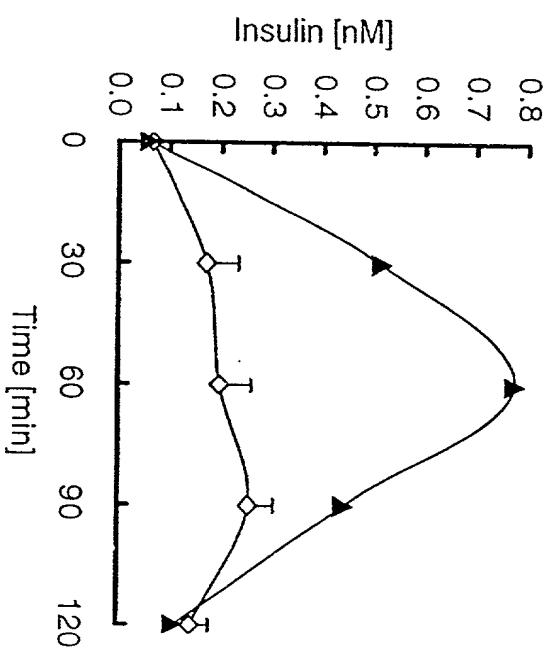


Fig. 18C

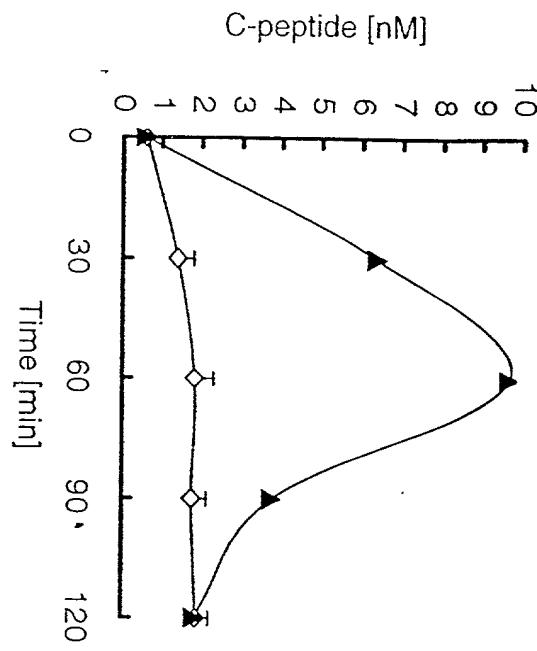


Fig. 18D

Fig. 14A

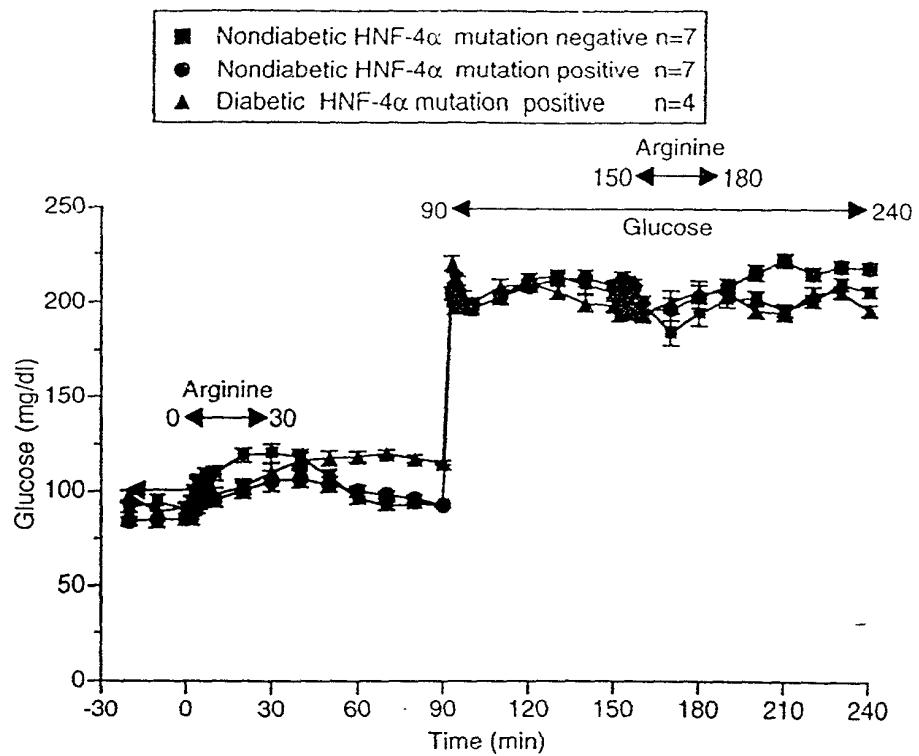


Fig. 14B

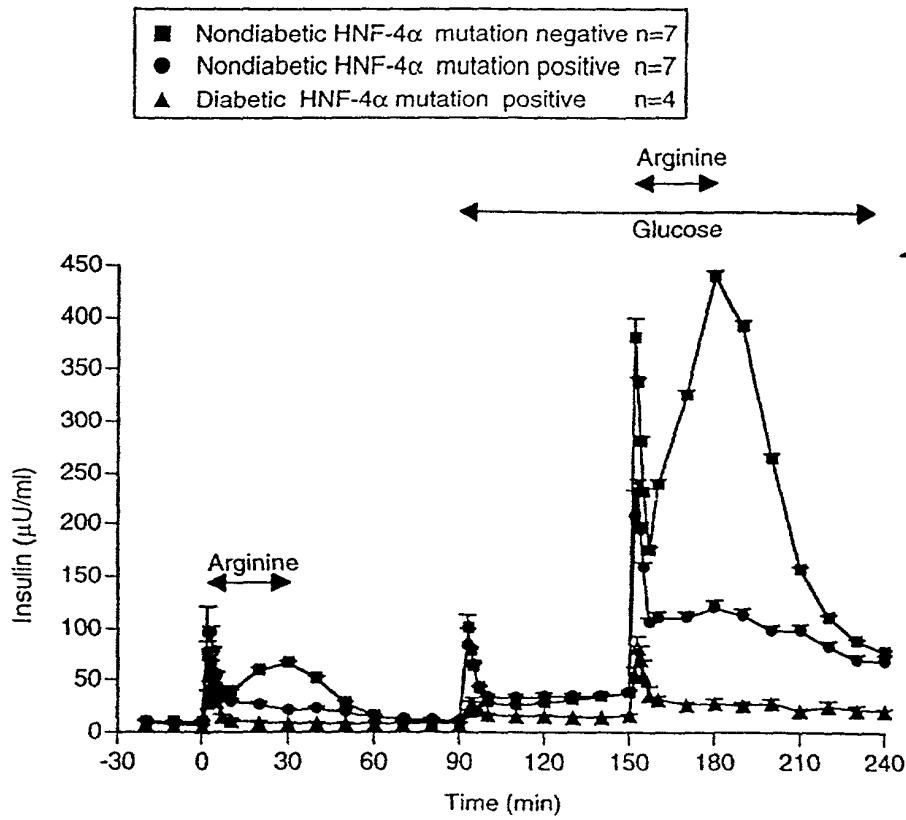


Fig. 14B

Fig. 19C

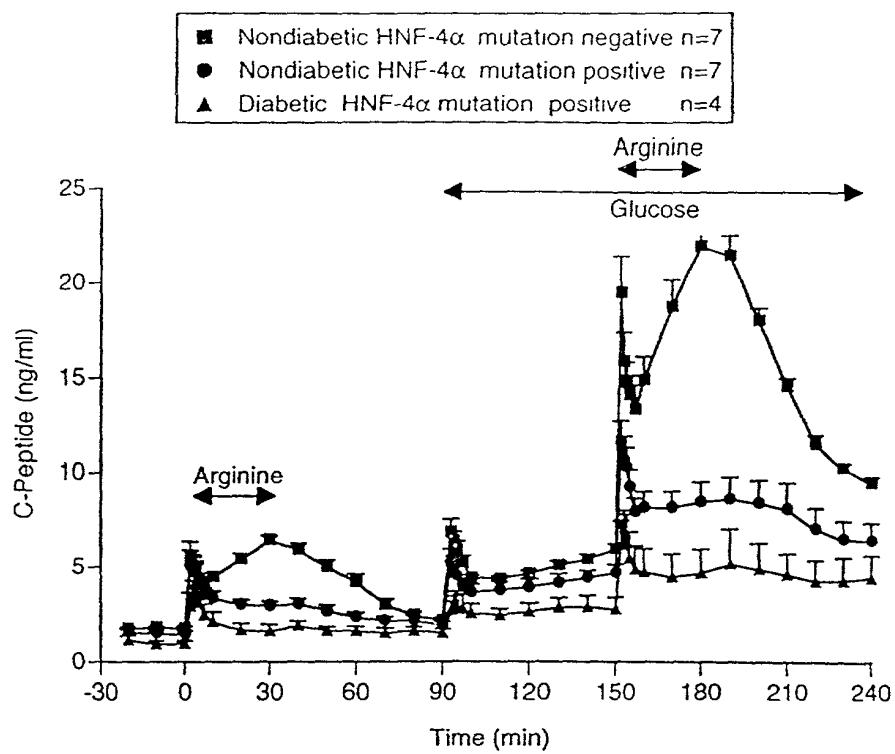
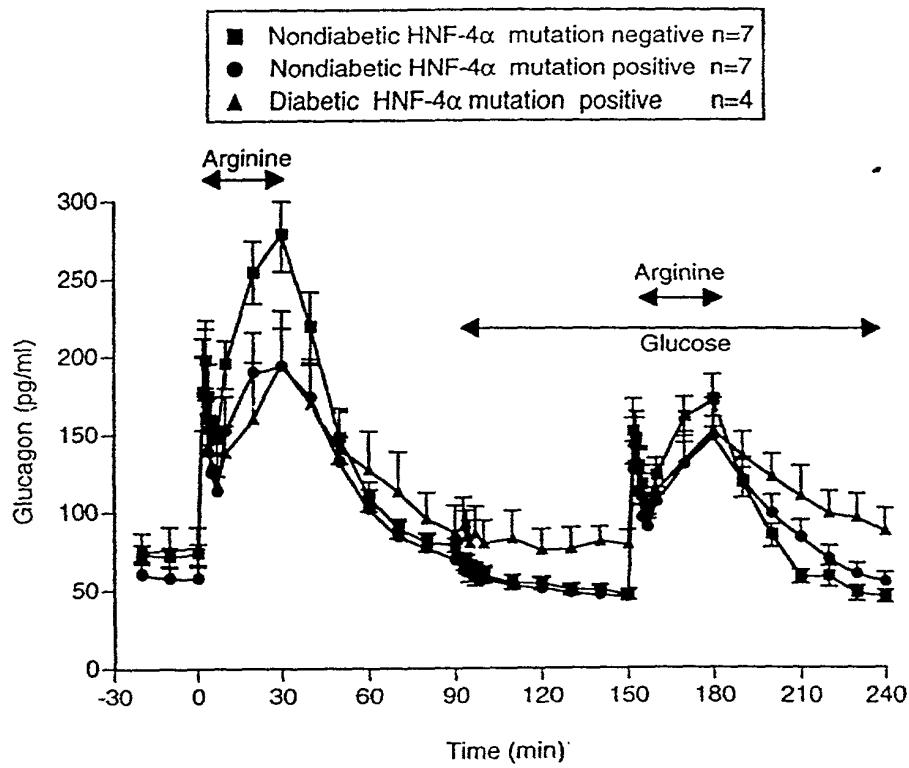


Fig. 19D



■ Nondiabetic HNF-4 α mutation negative n=7
 ● Nondiabetic HNF-4 α mutation positive n=7
 ▲ Diabetic HNF-4 α mutation positive n=4

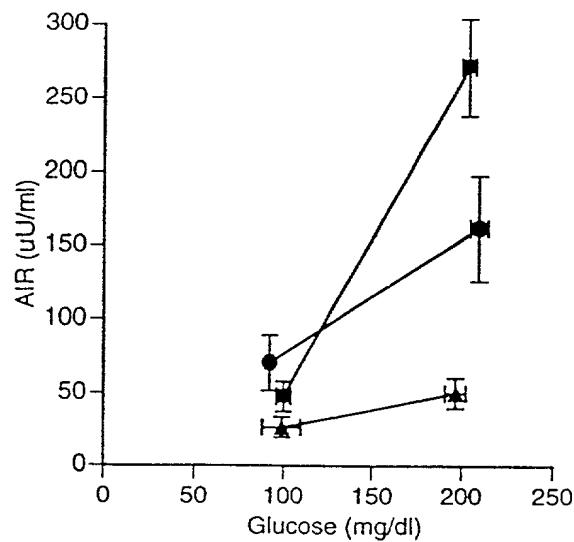


Fig. 20A

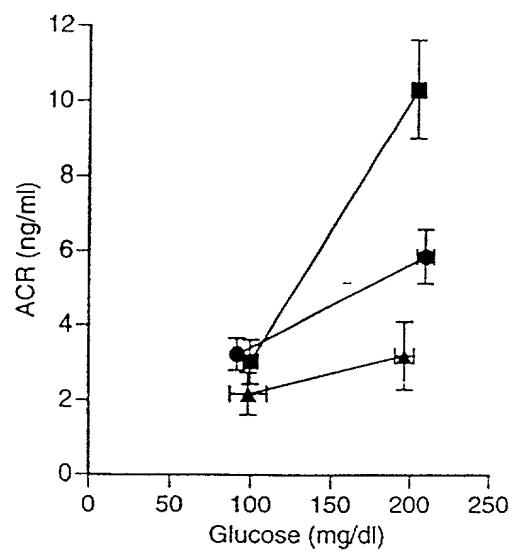


Fig. 20B

卷之二

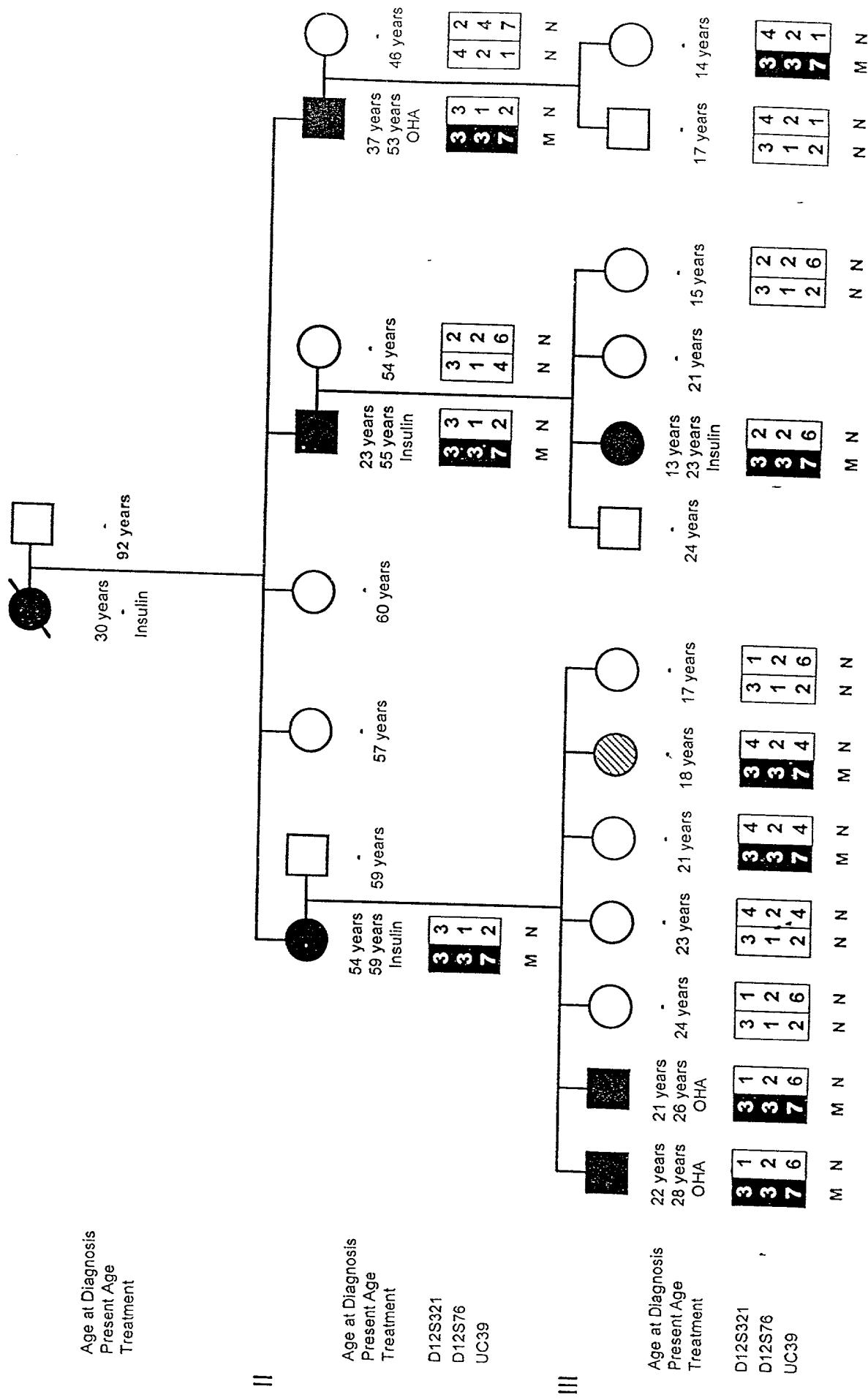


Fig. 22 A

Fig. 22 B

Fig. 22 C

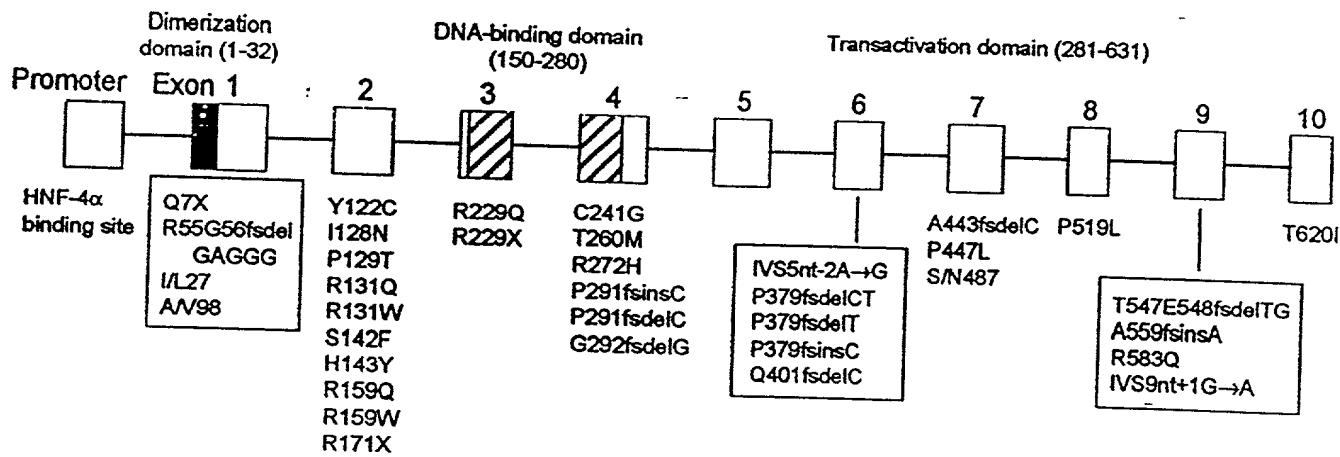


Fig. 23

J2-20

175 176 177 178
A AAG CAA NGA GAG AT
K Q R E
X
C/T

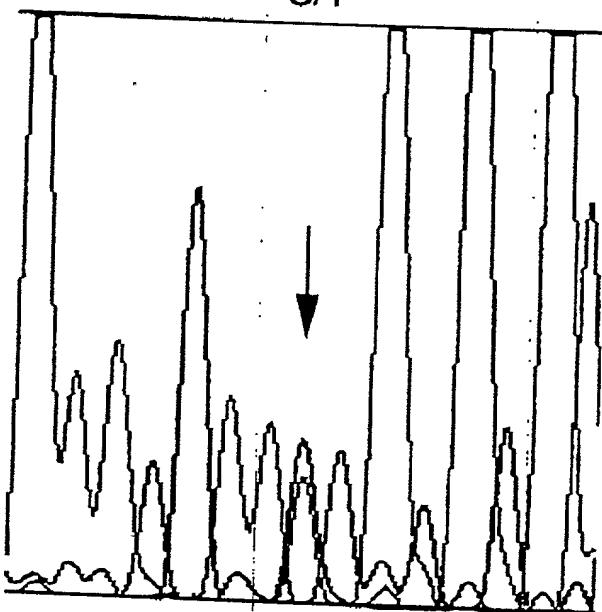


Fig. 24

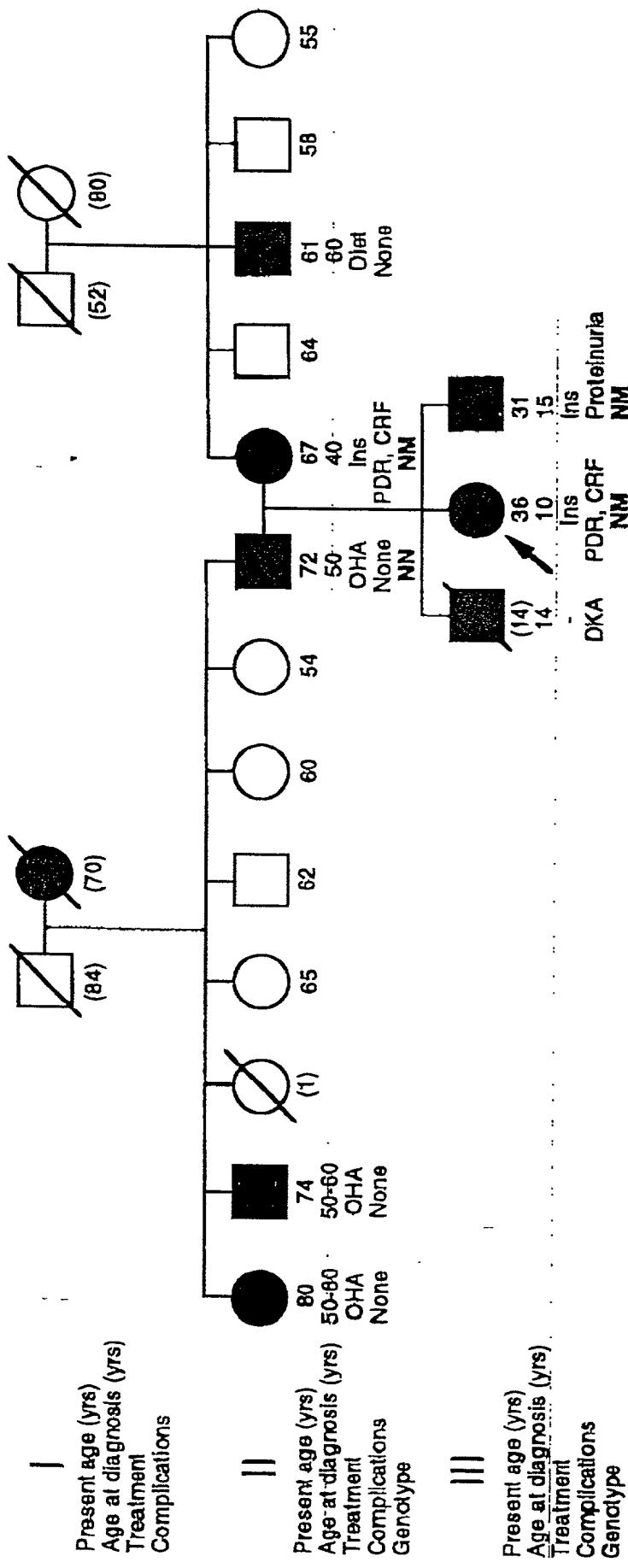


Fig. 25

1	AGCCAGCACCTGTTCTGGCACATGGTAATCTAACATATTTCCTACAGGGAGGCCCTGGTCAAGGCCGGAGTCAGGGAAAGGGTC	HNF - 3	AP1
91	CTAAATGGATGGAAGGGCCCCAAATGGCGTGGCATCCCTGCCCCCTGAGAAGAGCTAGCCAGCTGTCTAGAGCTTCTAGAGCTCCCTGCTG	NF1	AP4
181	CCGCTCTCGTAAGCAGCAAGCATTTCGGCCTCTGGCTCTGGCTCTGGCATGATGCCCTACAAGGTTCTGGGGTGGACCCAAACGCTGCT	NF1	AP4
271	CTCCTGATGGCTCCCTGGCTCCAGCTCCAGCTGGCTCAGGGCCCTCACTGGCCCTACCTGGCCCTACCCCTCCCTGCCCCAC	NF1	AP4
361	TCCCATGGCCTAGCTCCCTGCTCCCTGGCCATGGGCTGCACTTTGCAAGGTCAAGTCCAAAGTTCAAGTCCCTTCGCT	HNF - 3	HNF - 4 α
451	AGGCACACGGATAATACTGACCCCTGAGAAATTCCCAAGCTTCAATGTAACAGAACAGCCAGGGCCCTGATTCACGGGCCGCTGGGG	C / EBP	Exon 1
541	CCAGGGTTGGGGTGGGGTGGCCACAGGGCTTGGCTAGTGGGTTTGGCAAGGAGTTGGTGTGCTGCG	HNF - 3	AP1

FIG. 26A

631 GCGGCCAGCAACCCACGGCGTGGGGGGCTAACGGTGGTGGACCCGGCCGTGGCAGGCCGAGCCATGGTT
 SerLysLeuSerGlnLeuGlnThrGluLeuLeuAlaAlaLeuLeuGluSerGlyLeuSerLysGluAlaLeuGlyGlu
 721 TCTAAACTGAGCCAGCTGAGCTGGCCCTGCTGAGTCAGGCTGAGCAGAAAGGCCACTGATCCAGGCACTGGTGAG
C
G

ProGlyProTyrrLeuAlaGlyGluAspLysGlyGluSerCysGlyGlyGlyArgGlyGluAlaGluLeuProAsn
 811 CCGGGCCCTACCTCTGGCTGGAGAAGGGCCCTGGACAAAGGGAGTCCTGGGGGGAGCTGGCTGAGCTGCCAAT
 GlyLeuGlyGluThrArgGlySerGluAspGluThrAspAspAspPheThrProProIleLeuLysGluLeuGluAsnLeu
 901 GGCTGGGGAGACTCGGGCTCGAGACGAGACGGACGAGACGACTCAGGCCACCCATCAGACTGGAAAGACTTC
Va1

SerProGluGluAlaAlaHisGlnLysAlaValValGluThrLeuLeuGlyLysAlaValValGluThrLeuLeuGlyLys
 991 AGCCCTGAGGGGGCCACCAAGAAAGCCGTTCTCTGCA gtaaggaggccctgccccgtccccccgtccccccgt
T

FIG. 26B

FIG. 26C

FIG. 26D

FIG. 26E

2881 gtgactctaggcctgtaaaaggctgtccaggccggaaactccatgtatggatctgatggcattggccaggaaattgagaatacttgaacc
 c
 2971 taagcccatccctcgccggcccccctgcacccntggacaccaaaacccctccatgtatgcaccccaattggatttcataatcttcaatct
 3061 atggctcttttgcctcaactttatggatggaggactggatggatggatggatggatggatggatggatggatggatggatggatggatgg
 3151 cccagatctgcccaggctcaaaacctccggcaggntcagtttcataaccctcccttcatgcaggacagggttccttgagcctgg
 3241 cctggaggctcatggggcttctgcag GGGGAATGCATCCAGAGAGGGGTGTCCTCATCACAGGCCACAGGGACAGGGCTGGCTCCAAACC
**Exon 4 238 (Ar) gAlaGluCysIleGlnArgGlyValSerProSerGlnAlaGlnGlyLeuGlySerAsnL
 G (C241G)**
 3331 euValThrGluValArgValIrrAsnTrpPheAlaAsnArgArgLysGluGluAlaPheArgHisLysLeuAlaMetAspPheTyrSerG
 TCGTCACGGAGGTGGTGTCTACAACTCGGTTGGCAAAACGGGCCAAAGGAGAACGCTGGCACAAAGCTGGCATGGACACGTACAGGG
A (R272H)

FIG. 26F

3421 lyProProProGlyProGlyProGlyProAlaLeuProAlaHisSerSerProGlyLeuProProAlaLeuSerProSerLysValH
 GCCCCCCCCAGGGCAGGGCCAGGGGACCTGGCTTGCCCTGCGCTCACAGCTCCCTGCGCTCACCTGCCCTCTCCCCAGTAAGGCC
C (P291fsinsC)

3511 isG (ly) 319
 3511 ACG gtaagtggatgtggggacaaaggacaaatggggaaagggtggggaggactgtccattgacaggcagtccacctaaaccctc
 3601 ttgcacgttcaggttttccatttc::::: 2 kb :::::::gcagactgaccaggatggaaaaggtagaaacaaggcagatt
 3691 gctggctgcataaaaggcagacaggcagatggcttaaggcaaccatggaaatggatgttgaaggctgtggggcaggcaggcagg
Exon 5 319 (G) 1lyValArgTyrglyGlnProAlaThrSerGluThrAlaGluValProSerS
 3781 aagtgggtgtggcaggacactgtttccatccatccatccatccatccatccatccatccatccatccatccatccatccatcc
 3871 erSerGlyGlyProLeuValThrValSerThrProLeuHisGlnValSerProThrGlyLeuGluProSerHisSerLeuSerThrG
 GCAGGGGGTCCCTAGTGACAGTAGTGACAGTAGTGACAGTAGTGACAGTAGTGACAGTAGTGACAGTAGTGACAGTAGTGACAG

FIG. 26G

FIG. 26H

IleGlyProGlyGluProAlaSerLeuGlyProThrPheThrAsnThrGlyAlaSerThrLeuValIleG (1y) 437
ATCGGGCCTGGTGAAGCCTGGCTCCACGGTGCCTCCACCAACAGGTCACTACGTCATCG gtaaggctggggatgggt
4321 gggcacctgggtggaggctatggggcaaccgcanaatccaggagctggaaaagccactgggactcattcattcata
4411 caacatgt: ::::: 0.8 kb ::::::: taggagagggaggcagaactgacccccattggccctttgactgtgtgttacccagggttc
4501 cagggaaccgcaggcataacttttgaaacaaggtaaccgtttcccatatagcttagacaaagagctaaggctcagaggggaa

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Figure 1 continues on the next page

531

FIG. 26I

4591 atgacttgcacccacttaaaattttggcagggtcccgatggaggctgtttccctgaccacccctggcccttccaaaccacggggcc
 4681 tggggaggagggtgggtggcccttggggagggtcttggggagggtgggataataactggggccaggctgattccctccactccag
Exon 7
 4371 (G) lyLeuAlaSerThrGlnAlaGlnSerValProValIleAsnSerMetGlySerSerLeuThrThrLeuGlnProValGlnPheSerGlnP
 4771 GCCTGGCTCCACGGCACAGAAGTGCCGGTCATCAACAGCATGGCAGCAGCCCTGACACCCCTGACAGTCTCCAGC
T (P447L)
Ser
 4861 roLeuHisProSerTyrGlnGlnProLeuMetProProValGlnSerHisValThrGlnAsnProheMetMetAlaGlnLeuG
 CGCTGCACCCCTCTACCAAGCCGCTCATGCCACCTGTGCAGAGGCCATGTGACCCCTTCATGGCCACCATGGCTCAGCTGC
G

FIG. 26J

FIG. 26K

Exon 8 501 (A) IleLeuTyrSerHisIlysProGluValAlaGlnTyrThrHisThrGly
 5401 tcaggcacgtttgcccacgtctgccccctctcccccgtcgcccg
 CCTGCTCCGGAGACTATGCTCATACCGACACCAACCTGAGGCCCTGGCAAGCCACAGCAG gtaagggtccaggcc
A
 YLeuLeuProGlnThrMetLeuIleLeuAspThrThrAsnLeuSerAlaLeuAlaSerLeuThrProThrLysGln541
 5491 CCTGCTCCGGAGACTATGCTCATACCGACACCAACCTGAGGCCCTGGCAAGCCACAGCAG gtaagggtccaggcc
Exon 9 542 ValPheThrSer
 5581 tgctggccctccctcgccctgtgacagagccctcaccccccacatccccccggctcaggaggctcgctctgctccccccag GTCTTCACCTC
 rAspThrGluAlaSerSerGlyLeuHisThrProAlaSerGlnAlaThrThrLeuHisValProSerGlnAspProAlaGlyI
 5671 AGACACACTGAGCCCTCAAGTGACTCATCTCAGGCCACCAACCCCTCACGGCAGGACCTGCCCCAGGACCTGCCCCGAT
(T547E548fsdelTG)

FIG. 26L

FIG. 26M

PrF
 CATAACCCCGAAAGCTAGTAGTGTCTTCCTCGGACTAAAGCGGAACTGAGAACCGGTGAAAGCCCCGGCTAGGCTGCCAACAGTCCTAGGCTGCCAACAGTCAAGGTTAGGTGAGGTT
 GGCTGATAACGAGAACAGTAAAGAGGTGTCCTAGCCCCAGGCTGAGTCAATGACCCCTGGCAAAGCCCGCTCCGGCCAGGTCTGCTCNCAGGTCTGCCCTCCGGCTCT
 CCCCTCTCTCGGGTTCCCTCCACCATATGGCCCTTCCCACTAATTCGATCATCTATATGGCTTAATGGCTAAATGGCAAGTCTGCTGCTGCTGCTGCTGCTGCTGCT
 TTTCTGACTCTCTGGAGGCTCCGGACCGGGGAGTAACAGGGTCAAGGGCTGAGGGTGGAGGGTTCTGGATTTGGGTTGGCTGAACTCCCTCCACCTCTCCT
 1 Met Val Ser Lys Leu Thr Ser Leu Gln Gln Glu Leu Ser Ala Leu Leu
 Arg GTC TCC AAG CTC ACG TCG CTC CAG CAA GAA CTC CTC AGC GCC CTC CTG CTG
 Ser Ser Gly Val Thr Lys Glu Val Leu Gln Ala Leu Gln Leu Pro Ser Pro Asn Phe Gly Val Lys Leu Glu Thr Leu Pro
 AGC TCC GGG GTC ACC AAG GAG GTG GTG CTC GTC GTC CAG CTC GAG TGT GAG GAG
 Leu Ser Pro Gly Ser Gly Ala Glu Pro Asp Thr Lys Pro Val Phe His Thr Leu Thr Asn Gly His Ala Lys Gly Arg Leu Ser Gly Asp
 CTG TCC CCT GGC AGC GGG GCC GAG CCC GAC ACC AAG CGC TTC CAT ACT CTC ACC AAC GGC CAC GCC AAG GGC CGC TGG TCC GGC GAC

FIG. 27A

Glu Gly Ser Glu Asp Asp Asp Tyr Asp Thr Pro Pro Ile Leu Lys Glu Leu Gln Ala Leu Asn Thr Glu Glu Ala Ala Glu Gln Arg
 GAG GGC TCC GAG GAC GAC GAC GAC 115
 Ala Glu Val Asp Arg Met Leu Ser (r)
 GCG GAG GTG GAC CGG ATG CTC AG GAG GTG GAG GCG AGG GAG GGG GAC CCACCCG GAG GGG CTC GAG GAG GAG GCG GAG CAG CGG
 Ex1-2R
 AAGCCCGTTCACCAAAAAATTCCCCCGGGGGCCTCTGCTTCCTCCAAACACCCGGACCCCTTCCGACCTCTGAGGCTGAGTGAAGTGAAGTGCACACTCGCC
 CCAGGCCATCGTCC: 9 kb : :TCAGAAAGAACGGGATGAGGTGATCCGTACAGGGCAGTCACTCTCCCTGTTAGCTTCACTGCTACCCCCAA
 GTCCTAGCTTAGATGGGGAAAATTTCAGAAATTTCAGCATAGACCATAGGTAGCCATGGTAGCCCTAGAAAAGATGTTCTCCCACTAGTACCTAACCATCGCTTGCTG
 115
 2 (Sel)r Glu Asp Pro Trp Arg Ala Ala Lys Met Ile Lys GLY Tyr Met Gln Gln His Asn Ile Pro Gln Arg Gln Val Val Asp Val Thr
 CTAG T GAG GAC CCT TGG AGG GCT GCT AAA ATG ATC AAC AAG GGT TAC ATG CAG CAA CAC AAC ATC CCC CAG AGG GAG GTC GTC GAT GTC ACC
 Gly Leu Asn Gln Ser His Leu Ser Gln His Leu Asn Lys GLY Thr Pro Met Lys Thr Gln Lys Arg Ala Ala Leu Tyr Thr Trp Tyr Val
 GGC CTG AAC CAG TCG CAC CTC TCC CAG CAT CTC AAC AAG GGC ACC CCT ATG AAG ACC CAG AAG CGT GGC GCT CTG TAC ACC TGG TAC GTC
 182
 Arg Lys Gln Arg Glu Ile Leu Arg Gln
 AGA AAG CAA CGA GAG ATC CTC CGA C GAAAGTGTGTTTCATCTGCTCTGCTCAACCCATTGGCTCAGTTGCCCTCATGAC

FIG. 27B

AAGGCCCTGTGAGCACTGGAGATATGAGGAAGGTGGCAAGTAGATTGGCTTGGTGTGCTGTTGAGTGGATGGCTTCAGTCAGCCCCCTTGCTACCCAGC
 CAGTTGCTGTAGGAACTGGTGTAGTGT:::5 kb ::::: GATGGAGCPCACCCACTGACATCAAATPACAGGGTTAGGATGAGATGTTCACTGAGGGCCAGT
 GAGCCAAAGGGAAAAAATAATAATTAATTTCTTAAACTATAGCTGGCTATGTTGACTCTCCPTCAAAAGAAAGGAAAGGGTGGCTTGTGAGCACTGAGGGCTGTG
 CTGAGGGCTCCCATCTCCAGCTCACATGCAAGTGTGAAAGCTTACGTTAGCAGAGGAAATAACCTGAGAGGGATAAAACCTGCTGTGCTGTGCTGTGAGT
 182
 EX3F Exon 3 (G)ln Phe Asn Gln Thr Val Gln Ser Ser Gly Asn Met Thr Asp Lys Ser Gln Asp
 GAAGGCTACAGACCCCTATCAAAATCTACTCCCTCTCTCTTCAG AA TTC AAC CAG ACA GTC CAG AGT TCT GGA AAT ATG ACA GAC AAA AGC AGT CAG GAT
 (G)ln
 Gln Leu Phe Leu Phe Ser Gln Ser His Gly Pro Gln Ser Asp Asp Ala Cys Ser Glu Pro Thr Asn Lys Lys
 CAG CTC CTC TTT CTC TTT CCA GAG TTC AGT CAA CAG CCT GGG CCT GAT GAT GAT GTC TCC GAG CCC ACC AAC AAC AAG AAG

FIG. 27C

FIG. 27D

FIG. 27E

FIG. 27F

FIG. 27H

FIG. 271

1	TGGGTGGCTGTGACTGGCAGTACCCCCACAAAGCCCACCTGAAAGGTAGGAGACGGGTGGAGAGAAACAGGGGATGGCAAAGGG
91	GGATACGAAACAGGGAGGGGACGGGGAGGGATGGACGTCTACCGGGCCACTTGGTGTGTTATGCCATCTCATTCCTT
181	CTCAAAACCACCCCTTGAAAGTGTGATTGTACATTTACAGAAAAGGAAACTGAGGCTGGAGAGGAATACCCAAAGGTCTCCAGTTA
271	GTAGACGGTAGGTGCTGTGAAATTCAGGTCTCGCCTGTCGGGGTGGGTGGGATCACAGGGAGCAGGACGGGG
361	ATCCGAGATGGAGCCAGGCTGGCCAGAAAACACTGGAGCTGGGAGACGGAGGGAAACTGGAAAGGGGAAACTGGAAAGGGAGCTCC

FIG. 28A

541	CAGAACAGGATGCCAGAAGATGGCATCTGGGCTGGATTAGTTCTAAATCGGGCATGGGCAGGCCCTTATCTCGAAAGC	P1F →
631	ATTGAGGGTAGAACCTATGATTGGAAAGTTATTGAAATTAGGGATCTGGAGGTAGCTGGCTGAGTCAGTGCTGATACTGATAGAATG	HNF-6 →
721	CCTGACTTGGGTGACATGGCTTGAGGTAGGGGGTGGGTGAGTAAGGGTCAAATGAGTGGCCGTGAGTCATGATGCTGCCCTTGACATTG	P2F →
811	ATAACTGAACTCGTGAGTTAGGGCCCCAGCAAGCTGTAAATTAGCACCCGGGTGTCAGCCAGAAACCAAAACAA	HNF-3 →
901	GCCCCGCCAGCCTATCCACCGGGGGGACCCGATTCATTAACCCACCCCTCCCCGGAGAGGCCTCCACCCCCCTCACAGAGGCTA	HNF-1 α →
991	GGCCCAAGAACTCCAGGAGATCTTCCAGAGGGACAGGGTTCAGAAAGGAAGGAGAGGGAAGGCAACTGGGGAGGGCAGTGGGAGGGCG	ELF →
	A *	P1R ←

FIG. 28B

hrvalalaLeuLeuGlyalaatRPhisSerAspMetMet
 1531 CAGTGGCTCTGCTGGCGCTGGCAAGTGAATGATG
 1621 TCGTGAACCCCCCTGGGCTTAGGTTcAGAGAGACGGCAAGGGATGTTGAGATGGTGGTTGGAGACATAAACCGCATTCCTCGG
 1711 TGTCTTGGACTTTCTAGGGAAATTGGCACTTGGGAAAATGGAGCTCTCAAGGGAAAGTMTTGCTAACTACGAAGCCAACTCAG
 1801 CACTGTGTGTCTTGGCTCTGGTGTGTTGAGTGTGATAGTGAATGTTGCTGAGTTCTGGGTCTATTTCCTTGTATTCATGAGTGGGCTGTGTTGCTTAGGAGTT
 1891 ATATGCTGTTCAATTGTCCTCTGCTCTGCTGAGTTCTGGGTCTATTTCCTTGTATTCATGAGTGGGCTGTGTTGCTTAGGAGTT
 1981 GCCCGTGTGATCTTGTCTATGTTGTAAGTGTGTGACTTGTGTTGATGTTGCTATGTTGCTAGTGTGTGCTTGTGCTGGGGGT

FIG. 28D

2071 CATAGAGCACATGCCGTTGTGCATGCCGCCCTGCTGGACTTCTGCATCTCTGCTATGCCGTTTGTGCGTGTGCC
 E1BF →
 2161 CATATTGACCTGCTGTGTATATATGCAGTTCCTGCTGCTGCCGGGGGTCACGGCTCTGGGTGACTGACAGACAGACCCAAA
A
 2251 TGCAGGACCTCTGTTGCCACTCAACCAAGTGAGATTCAATATCAGCAAACATGTCGTTGGCTCTGAGCAG ATTTCGTTGCCCTGCGTC
 euAlaArgLeuArgLysProLeuArgLysHistidineSerIleSerGlyGlyValAspSerSerProGlnGlyA (sp)
 2341 TCGCCAGATTGAGGCATCCCTCCGACATCACTGGACCATATCTGGAGGCTGGACAGTCTCCACAGGGAG GTAGGGGGAAAAGAGGAGG
G

FIG. 28E

2431 CCCGGAAACCCCTCCGGAGGAAGGCCCATCGGTCCCAAGCCAGCCTCAGGGAGGGGGCAGCCAGCTGGCTGGCTAGGTCAAGCCTGC
 2521 CACCCCTGCTCCCTCTGTTGCTGGGCCACTAGCCAGTATGGCTCAGCTCCAGTGGTCTGGAATCTTGTGGTCAAGCTAGCTAGCT
 2611 ACGGTGAGGAGGCAGGTGGCACTGGCTGGTCTGCTAGCTCAGGGTGTGGCTCACCTGCCCTGCGTCCAGTCACGGTGTGGACGGCTTTAGGCTGTC
 2701 ATGTCACCTCCCTATCCTGGCTCTGTTATCTTCTACAAAACAGGCTCATTCAGGCTTCAGGCTGGCTGGCTGGAGTGGCTCC
 2791 TGAGGACCAAGGCCAGGGAGGCAAGGGAAAAACACACCAGAGAT: : : : : 4.4 kb : : : : CCCCTTGCGAGTTAGGGGGCTCC
 2881 CACCCCAAGGTGGCAGGGTTTCATGCCCTTCAGAGAAAGCTGGGGCTGGGGCTGGGGCTGGGGCTGGGGCTGGGGCTGGGGCTGGGA
 2971 AAGTCCTGAAAGTCACAAACCAGCCCAGTTACAGATGTGAAACTGAAGCTCCAAAAGTCAGGAGGTCACTGAGTGGGAGGTGATGGGA

FIG. 28F

3061	GTGGAAACAGCCCCAAGATCTGGCTGAGGCCGAAGCCCTGGAGATCCCCGCAAGGCCTGGCTGACATTCTGCTCTTCCTG	E2F →
3151	30 AACGCTCACTCCATCTCTCTGGCGAG ACACGTCCTCTCTGGCGAG	30 (A) spthr Ser ProSer GluglyThrAsnLeuAsnAlaProAsnSerLeuGlyValSerAla
3241	AGGCCTCACTCCATCTCTCTGGCGAG	AGGCCTCACTCCATCTCTGGCGAG
3331	uCysAlaLeuCysGlyAspArgAlaSerGlyAlaSerGlyAspGlyCysLysGlyPhePheArgArgSerValAla	uCysAlaLeuCysGlyAspArgAlaSerGlyAlaSerGlyAspGlyCysLysGlyPhePheArgArgSerValAla
3421	GTGTGCCATCTGGGGACGGGCCACGGGCCAAACACTACGGTGCTGAGCTGTGACGGCTCTTCGGAGGGCTGCG	GTGTGCCATCTGGGGACGGGCCACGGGCCAAACACTACGGTGCTGAGCTGTGACGGCTCTTCGGAGGGCTGCG

FIG. 28G

3511 AGAGCATCTTCTAGGAACACATTTACTGATCATCAAGCTACTGGCTGCCGTTATTGAGCTCTTATCATATGCCAGGCACAATACCA
 3601 AGTCCTTTGTGTTGTTAC : : : : 1.6 kb : : : : GTACTCCAGAGGTCAAGGTCTCCAACTCAGGCTCTAACACAAACCGAGAG
 3691 CGACCCAGGACACATGGTGCCTCTCTGAGCCTCAGTTTCCATGTTAGCAGGACAGGACTGGGCTCTTAGAGAGTCATAGCACCTT
 3781 TCCAGCTCCCTGGGGTTCAAGAGAGAACTCCGGATGAAGAGATGAAGAGACTGAGGTGGGGTCAACTGGATAACTGGGATAGCCAGGGCCCTA
 3871 GTCCTGCTCTAAGGGAGGAAGTTGTTCTCCATCCAAACCATCCAAAGCCTCCCCAG 88 (Ar) gPheSerArgGlnCysValValAspLysA
 Exon 3 FIG. 28H

3961 SPlysArgAsnGlnCysArgArgTyrxCysArgLeuIysCysPheArgAlaGlyMetLysLysGluA(1a)
 ACAAGAGGAACCAAGTGCCGCTACTGCAAGGCTCAAGAAATGCTTCCGGGCTGGCATGAAGAAGGAAG GTGAGCCTGCCCTCCUCGCCCC
 4051 ACCACCACTGCCAACCTGCACCCACAGCTCCCGGACAGTCATTACAAACTGTAGCCACACTTATGACTCAGTGGCAGGGCCCCAGGGTG
 4141 ACTGGCTAATGGCTGAGAAGGGGGAGGGCCTGAAATCTGACCATAGGGAGGGCTGGCTGGGTGCTTGAAGAAGATC: : : : : : : :
 4231 5.9 kb : :TCCCACCTCCTCATCAGTCACAGACACCCCCACCCCTACTCCATCCCCGTCTCCCTCCCTCACCTCTGTGCCTCCCTCAC
 E4F → E4F → Exon 4

FIG. 28I

120 (A) laValGlnAsnGluArgAspArgIleSerThrArgArgSerSerTyrgluAspSerSerLeuPheSerIleAsnAlaLeuGlnAl
 4321 AG CCGTCCAGAAATGAGGGACGGGATCAGCACTCGAAGGTCAAGCTATGAGGAAGCAGGACAGGAGCTGCCCTCCATCAATGCCCTCCTGCAGGC
 155 T(R127W) : (T/1130)
 aGluValLeuSerArgGln
 4411 GGAGGTCCCTGTCCGACAG GTACCGGGGTATCCTGCACCCACCCAGGGATCCCCACACTACAGGGAGCTACACTGAGTGGGGTTCACATGGCCCAGTT
 4501 TTCTCCCAAGCCAGGCCCTGGGAGCTGACGGGAGGGGGCCTCAGATAATTACAGAAAGGGACACTGAGTGGGGTTCACATGGCCCAGTT
 4591 GCAGGAAGGGCAGGAATCGAACCTGGGGCCTGGGGCACCTTCTAATTCATCCTACTGCTGCACTCCACAGGCCAAGCAAGTCTTCAC
 4681 CTTCACTGAGGGCCCTGCGATCACTCAGCTCCGAGAAACAGAGGAGTGGCAAGTGGGAGAGGAGTGGCTCAGTGGAGAGGAGTGGCAAAAGTGGGGCCAGGCCCTTC

FIG. 28J

FIG. 28K

FIG. 28L

5851 TCCAGGTTCTAGTTTATGGTAGTTRATGATGCCATTACAGTTACGGCAGGGTAGAGGCAGCGGAGGCATTAAAGCTGACTT
 5941 GCCCAGGGTCACTGACTTGGCTACGGGAGCCTTCCCAGGGTACAGATGGCAAACACTGTTCCRTCTCCTCTTCAG 198
 Exon 6 Val1AlaLeuLeuA
 E6F → Val1AlaLeuLeuA
 5941 GGGCCATGCTGGAGCACTGCTGGAGCCACCAAGGATCAGATCCTAGCTGCTGCTCTAG 237
 rgAlaHisAlaGlyGluHisLeuLeuGlyAlaLThrLysArgSerMetValPheLysAspValLeuLeuLeuG (1y)
 6031 GAGGCCAGGGCTCCAGGGAGGTATGCCCTAGCATGGCAACTACCAGGCAAGGAGATTCAATGGTGGCATGCAAGGGAGA
 6121 GGCCTGGCCAGGGCTCCAGGGAGGTATGCCCTAGCATGGCAACTACCAGGCAAGGAGATTCAATGGTGGCATGCAAGGGAAAT
 6211 CTAATCAGGAGTGGCCCTGCTCAGGCTGCAATTGGGGCTCCAGGACTCAACTGGTACCCCACTCAGATGCCAAGGAAAT
 6301 GTCGATGCAAGTCACCAAATCCCCAGCATTAAGTCAGGCACGATCAGGGTTATCCCTGGAAATTACCTGTGCATCCCTTTCTTTGA

FIG. 28M

6391 CAGAGGTCTTGCTCACTCAGGTGGAACTGATGTGA: : : : : 1.4 kb : : : : : GCAAAACACTACCCATTATTAATAACA
6481 ATGGCTATGGGAGCTCGATTTATTTATCCTCATCTTATAGATAAGAAAACCTGAGGCACAGAGGGTAAGTAACCTTATCCAACCTATAACC
6571 AGCTATCAGGGGAGGCCATTAAAGCAAGGGCAGTGCAGTTCCAGAATCTGGTCTTAACTTAACTTAACTGCTGATGCTTGGTGCCTATCAGGTGACC
6661 TTGGAATGTCATCGATCTTGAGTCATGTGGTAATGGAGCTGGTCAATGTGAAGAGGTCTAGAAAGGCCAAGTTCCAAGGCTCAGC
6751 CGGATGACTCAAGGAGCTTATCTCTGAATCTGGGCTCAGCTTCCCTAACCTGAAATGGGAGTCACCATCCCTGCAAGGTCTCCCTCC
6841 CACAGGCCACCAACTCTTGCCTAAAGCCAAACTAGAGGAAGGGGTOACCCAAGGTGACTTCCATCCTCCCTCCCTCCCAA

E7F $\xrightarrow{\quad}$ _____

FIG. 28N

FIG. 280

FIG. 28P

7831 gSerGlnValGlnValSerLeuGluAspTyrIleAsnAspArgGlnTyrAspSerArgGlyArgPheGlyGluLeuLeuLeuLeuLeuPr
 TrCCAGGGTGCAGGTTGGAGACTACATCAACGACCCAGTATGACTCGCGTGGCTTGGAGAGCTGCTGCTGCTGCTGCC
 otherLeuGluSerIleThrTrpGlnMetIleGluGlnIleGlnPheIleLysLeuPheGlyMetAlaLysIleAspAsnLeuLeuGlnG1
 CACCTTGAGAGCATCACCTGGCAGATGATCGAGCATCCAGTTCATCAAGCTCTGGCATGGCAAGATTGACAAACCTGTTGAGGA
 368
 uMetLeuLeuGlyG (ly)
 GATGCTGCTGGAG GTCCGTCCAAGCCCAGGGAGGGGGGGGGGGAGCTGGAGTGGAGTGGAGCTGGAGAGCTGGAGCTCACC
 G P C Q A Q E G R G W S G D S P G D R P H T V S S P
 8011 CCTCAGCTCTTGGCTTCCCCACTGTGCCGGCTTGGCAAGTGCTTAACCTGCTGCTCAGTTCCCTCACAGAAAATGGAAACA
 L S S L A S P L C R F G Q V A

FIG. 28Q

8191 AGGCAATGGCTTATTGTTTCAGGCACCGAGAACCTAGCACGGCOAGTCACTGTTCTAAGTGCTGGCAATTAGCAAGAACAGATCTT
8281 TGCCCTCGGGAGGCTGTGTGAGTATGTATGGATGCCGTATGTGTATATGCCGTATGTGTATGCTGATCTGTTATAAAAG
8371 CCTCACATTATGATTGAAATAAACAGGTAATATGA: : : : 4 . 4 kb : : : : GGGACACATAGATGCTATAAGTACGTCAGTT
8461 GGCTGCAGCAGAGATGCGGATGAGGCTGAAAGGTGAGGGACCAATGGTTGAGGACTTGCACTCCAAGGAGCTTGAGAGCCA
8551 TTGATTACATCCATTATTTACTATGTGACCAATACATTACAGCTTACGAAACATTAGAAGCTAGCTGATTCAGGCTTATATGCACTTGT

FIG. 28R

8641 CCTTTCAACTCACTTTGGTTCTCTGGGCTCTCTTAACACCCCTCATGAAGTCATAAGATGGGAATGGTACACCCCTAGTTA
 8731 CTAACCCAGGAATAGGTACCCAACAGGCACCTGCCAATATTGGATGGGCTGGTTGATTGGCCACGCCCTGAGGAAGATGGCGTCCCAAGGCC
 8821 TGAGGTCTGCATCCAGACTCTCCATCCTGATCGACCTCTACCTGCAG 368 (G) LysSerProSerAspAlaProHisAlaHiShiSProLeuHi
 isProHisLeuMetGlnGluHiMetGlyThrAsnValIleValAlaAsnThrMetProThrHiMetCysGlnAsnGlyIleSerAsnGlyCysGlnMetCysGln
 8911 ACCCTCACCTGATGCCAGAACATATGGAAACCAACGTOATCGTGCAACACATGCCCAACTCACCTCAGCAACGGACAGATGTTGAGT 419
 rpproArgProArgGlyGlnAlaA (1a)
 9001 GGCCCGACCCAGGGACAGGCAG 419 GTGGGCAAACTCTGGGATTACCTTGCAAAGGGTTAAGACAGGGCAGGAGA

FIG. 28S

9091 AAGTGGAGCTAACAGTAGAACCAACAGTTCTGGGTTCCAGGTAGGGATAAAGGGCAAGATTGTCATTTGTTGAGGC
 9181 TGTTTATCAGTAAAGGTGACTGACAGGCCCTTACTGAATGAAAGCCATTGTTGGATGAGGTAACCCATTTGGGTG
 9271 AAGATGCTTGGGTGAGAATTCCATTAGTTGACATTGTCATTTAGTAAAGTGGTCATTGAAAGTAAAGCTGCAAGTTGGGTAAAGGCTA
 9361 TCCATTAAGACATTAGATGAGACTACCCATTGGTCAGGATGTCCTGGCTGA::: 1.4 kb :::::TTTGGGAGAAGCAGTCC
 9451 AAGTCCTGCATATCAAATAATGATGGAGAGATGGGTGGTAGGACCTTCAGACCTCATAAAACCTTATGATCTGGGACTCACA

FIG. 28T

9901 CCCAGCCCCCTTAAGAGAGCACCCTGGTGATGAGCTGGTACGGCAACGGTACGGTACGGCAAGGAAAGTGATGCCAGAGCAGAGCAGGAATGGGAAG
9991 GATGAAAGGGCCGAGAACATGGCCCTAACGGACATGCCACTGCACCCCTGACGCCCTGCTGATAACAAAGACTTTGACTTGGGGAGACCCCT
10081 CTAATGCCCTTGACAACTTCTCATGTTGAAGCCACTGCCTTCAACCTTCACCTTCATCCATGTCCAACCCCCGACTTCATCCCAAAGGAC
10171 AGCCGCCCTGAGATGACTTGAGCCCTAAC

FIG. 28V